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A NEW METHOD FOR DIFFERENTIAL STAINING OF PLASMA CELLS AND OF OTHER BASOPHILIC CELLS *

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The methyl-green pyronin mixture of Pappenheim and Unna, while serving a useful purpose in the staining of basophilic cytoplasmic substance in numerous varieties of cell, suffers a certain diminution of value, in that for the securing of best results preliminary fixation of the tissue in absolute alcohol is requisite. Material fixed in Müller's solution plus formaldehyde can usually be satisfactorily stained after subjecting the slides to a preliminary soaking in alcohol; but the use of other reagents is as a rule followed by failure. The more frequent use in this laboratory of Zenker-acetic acid solution for routine fixation has led to a search for another formula by the use of which there might be secured comparable differential staining of material so treated. Stropeni [1] stated that the substitution of acridine red for pyronin accomplishes this result, and presented two formulae for preparing the staining mixture. Attempts in this laboratory to utilize his methods have been unsuccessful, in that uniform overstaining by the red dye has constantly occurred. Efforts to overcome this defect by reducing the relative amount of the acridine red or by lengthening the period of differentiation have resulted merely in complete failure of differential staining. In view of the fact that even in successful Unna-Pappenheim preparations, the nuclear staining is rather weak, it was felt that the substitution of another nuclear dye for the methyl green might be of advantage. Malachite green was tested and was found to answer the purpose admirably.

The staining fluid finally adopted consists of a mixture of a 2 per cent aqueous solution of malachite green with a 2 per cent aqueous solution of acridine red, in the proportion of one part of the former to three of the latter. This mixture keeps well and does not show any

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† With the technical assistance of Jessie C. Hon.

1. Stropeni, L.: Una nuova miscela per la colorazione delle plasmazellen, Ztschr. wissensch. Mikr. **39**:302, 1912.

precipitation. A few weeks' ripening of the mixed solutions is of advantage, though excellent results are secured when the stain is employed as soon as prepared. Only Grűbler's dyes have been used. Sections prepared by the paraffin method are passed through iodine in the usual manner. The iodine is removed by graded alcohols followed by thorough washing in running water for at least fifteen minutes; incomplete removal often results in precipitation of the stain. The slide is then flooded with the dye solution for from fifteen to thirty seconds.

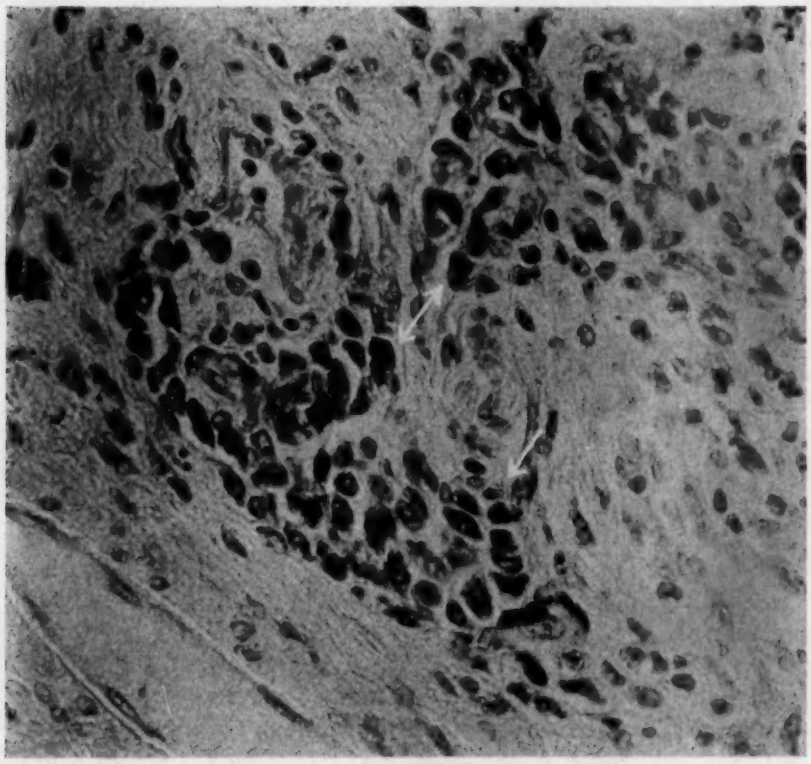

Fig. 3.—Another portion of the same tonsil as in figure 1, showing perivascular infiltrate containing basophilic cells and particularly rich in plasma cells; × 560.

The excess of solution is drained away, and the slide is rapidly washed in water. It is then passed directly into absolute alcohol, where it is left only as long as the dye continues to be washed out in clouds. It is then transferred quickly into xylene. Occasionally, the brilliancy of the preparation is enhanced by restaining.

Comparative observations have shown that alcohol-fixed material is well stained by this method, but such sections are more deeply colored by the Unna-Pappenheim formula. On the other hand, tissue fixed in corrosive sublimate or in Zenker-acetic acid solution yields better prepa-

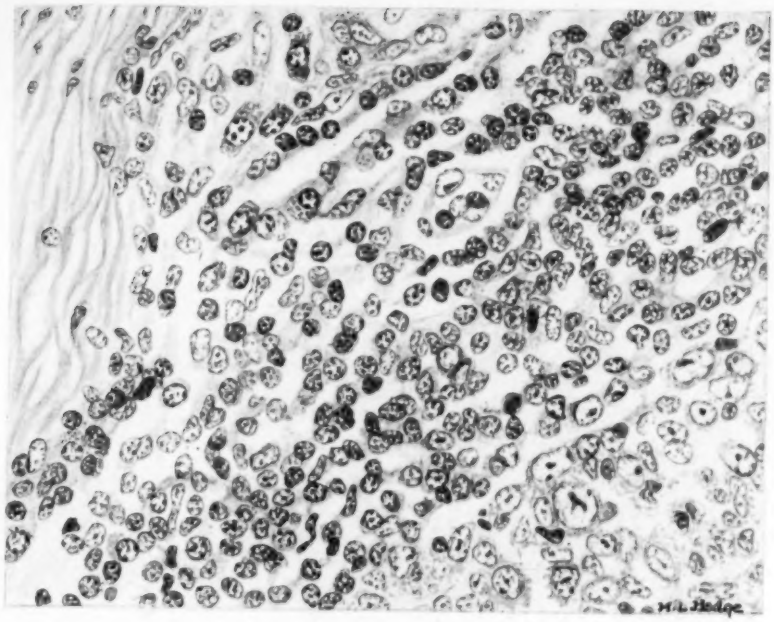

Fig. 1.—Section of tonsil from patient with rheumatic fever. Plasma cells in margin of lymphatic tissue. "Germinal center" in lower right hand corner. All sections are stained by the malachite-green acridine-red method. This section is here magnified 750 times.

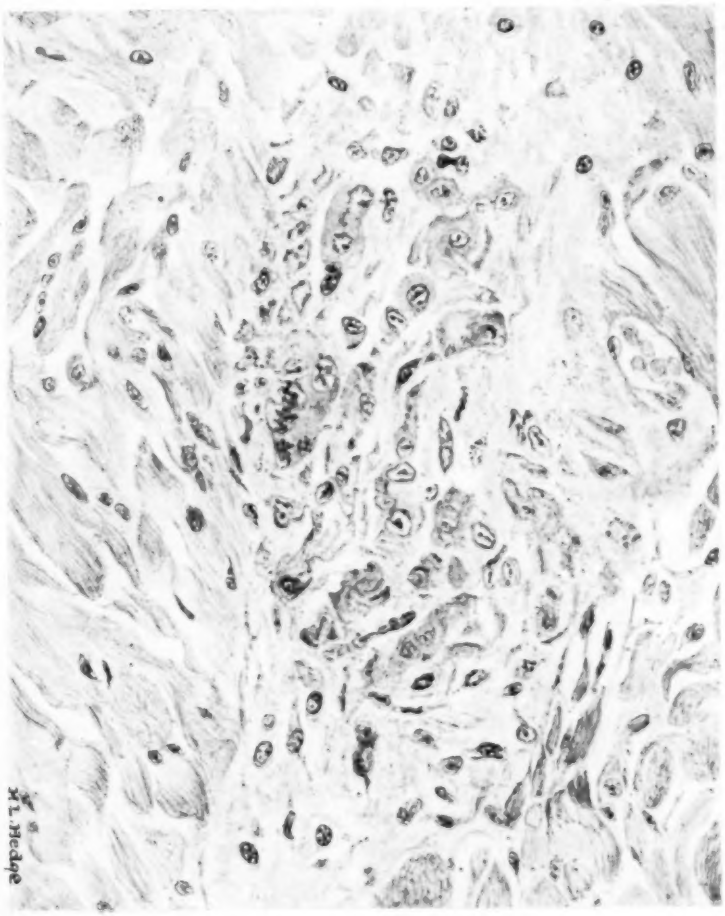

Fig. 2.—Aschoff body in heart muscle of patient dying with rheumatic fever; × 450.

rations when the malachite-green acridine-red mixture is employed. Results in fixation with Müller's solution plus formaldehyde have been unsatisfactory, even when the slides have been subjected to preliminary overnight soaking in alcohol.

This method presents certain advantages in addition to its applicability following Zenker-acetic acid fixation. The brilliancy and depth of color of a successful pyronin stain tend to obscure detail, and in addition there is usually a certain degree of pink color throughout the section.

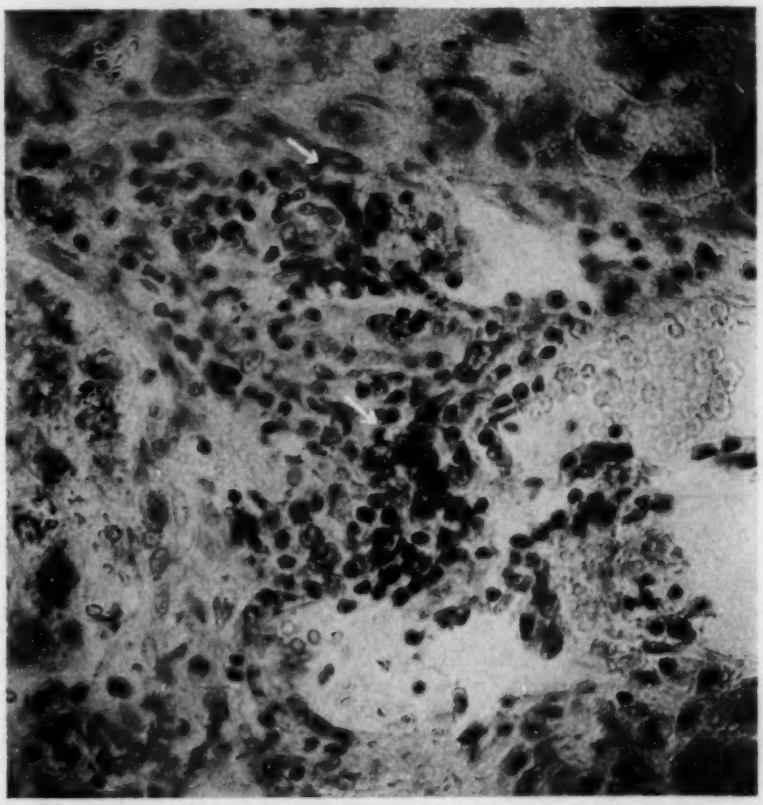

Fig. 4.—Experimentally produced perivascular exudate in rabbit's liver; × 560.

Acridine red, while not yielding the same depth of color, does not cloud the picture, even when minute detail is studied with the oil-immersion objective. There is no confusing background of pink, so that the differential staining of the basophilic substance, while more delicate and of a lighter hue, is just as distinctive as in the case of more deeply colored preparations. Furthermore, the superiority of malachite green over methyl green as a nuclear stain is highly advantageous. While

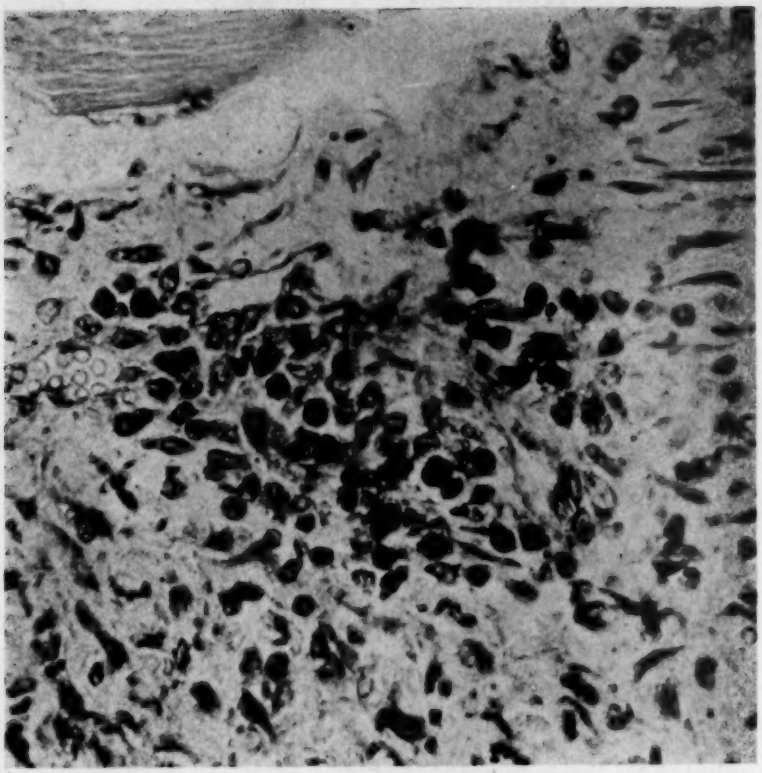

Fig. 5.—Infiltration around infected agar focus in subcutaneous tissue of hyperergic rabbit; × 560.

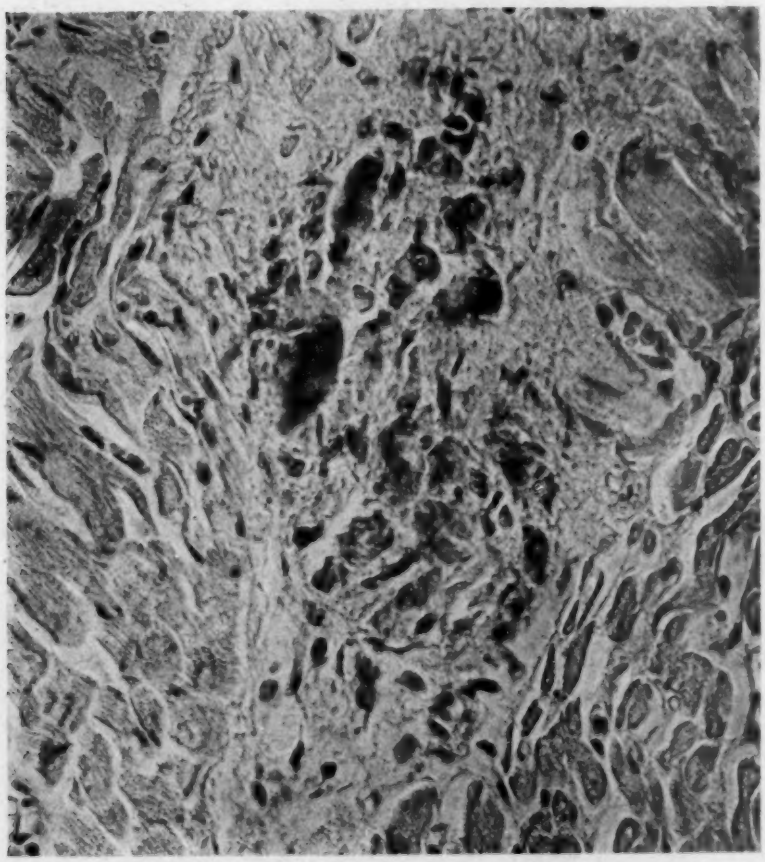

Fig. 6.—Same Aschoff body as in figure 2; × 470.

not so detailed as that secured by the use of iron hematoxylin or of safranine, the delineation of the nuclear structure is sharp and clear, and provides an excellent contrast with the various shades of cytoplasmic red. Certain other structures are stained by this nuclear dye, as, for instance, striated muscle, fibrin and certain pigments.

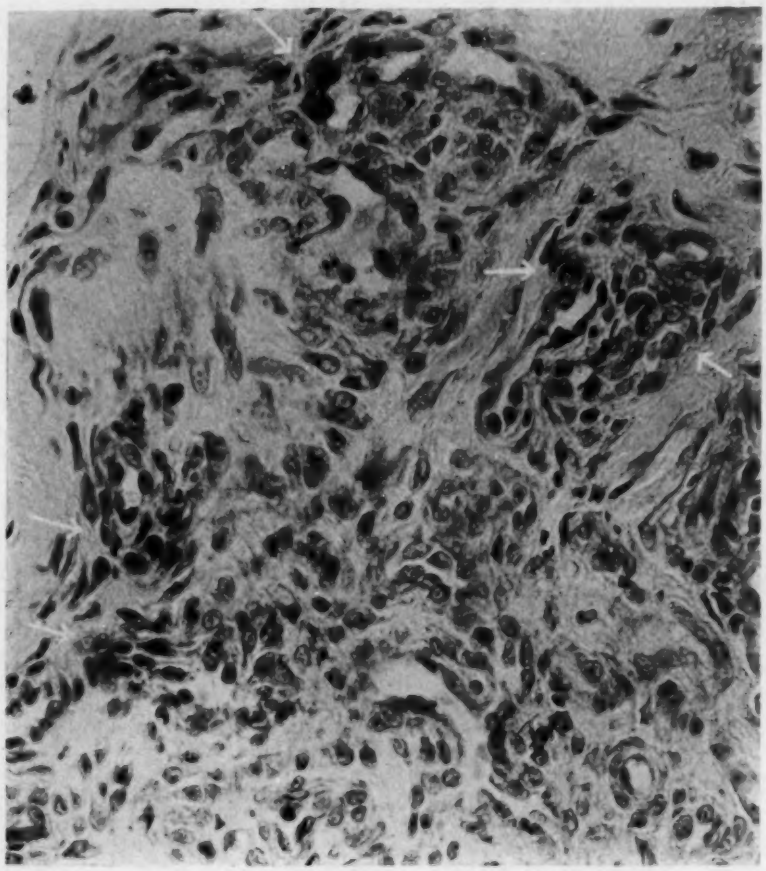

Fig. 7.—Subcutaneous nodule removed at biopsy from patient with rheumatic fever. Various degrees of tissue basophilia are present; × 470.

Results par excellence are secured when lymphatic tissue is prepared by this method. In the colored figure 1, which is derived from a specimen of tonsil, the deep hue of the plasma cells, contrasting with the lighter and brighter tint of the large cells of the so-called germinal center, is well seen. Nuclear detail is clear and sharp. In the photomicrographs, it is of course difficult to portray the differential staining to the same degree, but comparison of figure 3 with figure 1, both from

the same slide, will aid in the interpretation of the former. Other basophilic cytoplasm, such as that of many young or functionally active cells, is colored in various shades of red or pink. Ganglion cells are deeply stained; so also are many of the immature cells of bone-marrow. In figure 4 is pictured an experimentally produced perivascular infiltration within which basophilic cells are present and can easily be identified. Figure 5 represents a hyperergic tissue reaction in which many deeply basophilic cells are present.

The cytoplasm of the characteristic cells of the Aschoff body is stained a rather dull, smudgy red, which varies considerably in depth from cell to cell, and is distinct in quality from the brighter hues seen in young or functionally active cells (compare figs. 1 and 2). This peculiar tone-quality was noted by Aschoff [2] and by him was ascribed to degeneration of the cell. In young subcutaneous rheumatic nodules may be found great numbers of basophilic cells, some with brilliantly staining protoplasm, others characterized by the dull dirty red of the Aschoff's body cell. Similarly staining cells are frequently encountered in other rheumatic tissues. The peculiar dulness of color noted in many of the cells of rheumatic tissue is rather distinctive, and it seems possible that systematic investigation with this method may shed further light on the disputed questions of their origin and nature. Figures 6 and 7 and the colored figure 2 reveal more fully than any description the exactness of detail secured by this method, and its applicability to study by high magnification.

SUMMARY

By the use of malachite green and acridine red, the Unna-Pappenheim staining method has been so modified as to be applicable to tissue fixed in Zenker-acetic acid solution. Such preparations are better adapted to study by high magnification. This modification is particularly valuable in the study of lymphatic tissue and of rheumatic fever material.

2. Aschoff, L.: Zur Myocarditisfrage, Verhandl. d. deutsch. path. Gesellsch. **8**:46, 1904.

OXYURIS VERMICULARIS IN THE PERITONEUM *

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Infection of the peritoneum with *Oxyuris vermicularis* is not a common disease, and the following case illustrates the difficulty of diagnosis at operation. The surgeon made a diagnosis of tuberculous peritonitis at laparotomy and sent a nodule to the department of pathology for histologic section. The tissue proved to be *Oxyuris vermicularis* walled off in the peritoneum.

REPORT OF CASE

A married woman, aged 21, entered the hospital on April 25, 1928, complaining of the continuous passing of urine through the vagina, beginning with her last delivery six months before. The only other complaint was amenorrhea, which also began at that time.

The physical examination showed nothing abnormal, except that there were only vestiges of the urethra left. A fistula admitting one finger opened from the vagina into the base of the bladder. This fistula was surrounded by dense scar tissue. Beyond the fistula, the vagina appeared as a narrow transverse slit between rigid cicatricial lips. The patient was advised to have a transplantation of the ureters into the colon.

In the course of ureterocolostomy, several loops of small intestine were found covered with hard white nodules, each slightly smaller than a pea. These nodules were diagnosed as tubercles. One was excised, fixed in Kaiserling I solution, dehydrated, embedded in paraffin and stained with hematoxylin and eosin and Gram's stain. On microscopic examination, the tissue showed two cross sections of a female oxyurid filled with eggs (fig. 1). The wall of the parasite was clearly outlined, and the two lateral spurs helped to identify it. Immediately surrounding the worm was a zone of degenerating tissue, in which no definite cellular structure could be made out. The outer zone was made up of concentrically arranged connective tissue cells, among which were eosinophils and histiocytes. No giant cells were found around the parasite and no bacteria were found by the Gram method.

A few cases of *Oxyuris* encapsulated in the peritoneum similar to the one described now are reported in the literature. At the autopsy of a 42 year old woman who died of carcinoma of the breast, Kolb [1] found ten hard nodules on the peritoneum of the pelvis. These nodules were white, the size of grains of rice, and some of them were pedunculated. With the exception of one *Ascaris lumbricoides* in the esophagus, there were no parasites of any kind in the gastro-intestinal tract. The

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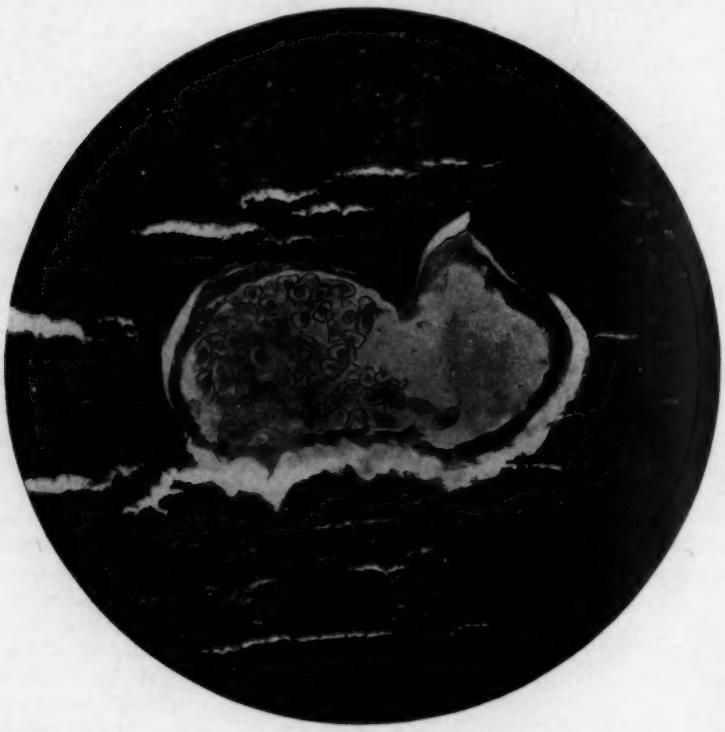
1. Kolb: Centralbl. f. Bakteriol. (Orig.) **31**:268, 1902.

mucosa of the rectum was normal, and the vagina, uterus and tubes showed no changes. Microscopic examination of the nodules showed numerous ova of *Oxyuris vermicularis*. Schneider's [2] case was similar. At the autopsy of a 36 year old woman who died of diffuse peritonitis after a hysterectomy, he found a nodule 2 cm. in diameter near the operative stump of the left ovarian ligament, which showed a mature oxyurid surrounded by connective tissue and containing ova. Marro [3] reported a case of an oxyurid found at autopsy in a 34 year old woman



Section of Oxyuris vermicularis showing ova.

from an insane asylum. Two small growths were situated on the outside of the left tube near the fimbriated end, one the size of a pea and the other twice as large. In situ, they were thought to be the remains of an old peritonitis. Both were cystic, containing clear cholesterol crystals in fluid. The smaller one contained numerous ova of *Oxyuris*. Histologic examination of the cyst excluded the possibility of a direct extension through the wall of the tube. Strada [4] also found an encap-

2. Schneider: Centralbl. f. Bakteriol. **36**:550, 1905.
3. Marro, G.: Arch. per le sc. med. **25**:161, 1901.
4. Strada, F.: Arch. per le sc. med. **31**:418, 1907.

sulated oxyurid on the peritoneal surface of the pouch of Douglas in a 60 year old woman who had died of bronchopneumonia. Schroeder [5] reported a similar case. Kaufmann [6] found *Oxyuris* in tissue from a 31 year old woman removed during laparotomy.

The chief question concerning these cases of encapsulated *Oxyuris* on the peritoneum has to do with the mode of entrance into the peritoneal cavity. There are two possibilities: one is by way of the genitalia in females and the other is by direct extension through the wall of the intestine. It is agreed by most writers that the oxyurid gains access to the peritoneal cavity in females by way of the vagina, uterus and tubes. This seems logical because oxyurids have been found in all of these at different times. Heller [7] found oxyriuds incidentally in the vagina at autopsy, while Spitzer [8] found many living worms (oxyurids) in the solution following a vaginal douche in a 12 year old girl. Westphalen [9] mentioned having seen these parasites near the cervix. Simons [10] found them living and motile in the cervix of a living woman, and Vix [11] reported that he found the eggs in uterine secretions.

The only instance in which the uterus was found to be infected was the case of Benedetti [12] in which he found *Oxyuris* between the placenta and the uterine wall.

Chiari [13] found the female parasite surrounded by giant cells in a tube with salpingitis of long standing. He assumed that the parasite gained entrance to the tube by way of the vagina and cervix, because *Oxyuris* had been found in these locations. Tschamer [14] found two living oxyurids in the right tube of a 31 year old woman.

It will be noted that all the cases of encapsulated oxyurids in the peritoneum were in women. Entrance to the peritoneal cavity by way of the genitalia seems reasonable. However, there are certain cases in which abscesses caused by *Oxyuris* have been found in the intestinal wall, and these cannot be explained in the same way. Nathan [15] reported a case in a young workman with a perirectal abscess in which

5. Schroeder: Lehrbuch der Gynäkologie, ed. 2, Leipzig, F. C. W. Vogel, 1926.
6. Kaufmann: Lehrbuch der speziellen pathologischen Anatomie, Berlin, W. de Gruyter & Company, 1922, p. 672.
7. Heller: Deutsches Arch. f. klin. Med. **77**:21, 1903.
8. Spitzer: Wien. med. Wchnschr. **42**:6, 1892.
9. Westphalen, cited by Kolb (footnote 1).
10. Simons: Zentralbl. f. Gynäk. **23**:777, 1899.
11. Vix, cited by Kolb (footnote 1).
12. Benedetti, cited by Kolb (footnote 1).
13. Chiari, H.: Virchows Arch. f. path. Anat. **269**:730, 1928.
14. Tschamer: Zentralbl. f. Gynäk. **43**:989, 1919.
15. Nathan: Frankfurt. Ztschr. f. Path. **36**:82, 1928.

he found the eggs of *Oxyuris* but no bacteria. Weigmann [16] and Froelich [17] cited similar perirectal abscesses in two boys 6 and 11 years old, respectively. Dmitrieff [18] reported a case of intestinal obstruction as a result of a partly perforated abscess due to *Oxyuris* in the colon. The appendix was normal but filled with oxyurids. Hippus and Lewinson [19] found *Oxyuris* under the serosa of the appendix of a 6 year old girl. They also found eggs of *Oxyuris* in contiguous lymph glands. There were no bacteria in the wall of the appendix in this case. The parasites must have traversed the intestinal wall in these cases. If they went through an opening in the wall passively, all the abscesses should contain bacteria, as well as the oxyurids. With the present data, however, it seems impossible to draw any definite conclusion.

The pathologic effects of encapsulated oxyurids in the peritoneum are not grave, according to Strada, who drew this conclusion from the cases which he found described in the literature and from his own case. The same is true of the case here reported, for the patient has had no further symptoms referable to the remaining nodules in the peritoneum. It appears that the parasites entered the peritoneal cavity bringing with them few if any bacteria from the genital tract. The peritoneum reacted against the worms as it would react against any foreign body, by encapsulation.

SUMMARY

A case of *Oxyuris vermicularis* encapsulated in the peritoneum is reported, and a review of reports of similar cases is given. All the seven cases reported have been in women. Since oxyurids have been found in various parts of the genital tract, it is concluded that they gain access to the peritoneal cavity by this route. No serious pathologic effects have been noted from the encapsulation of *Oxyuris* in any of these cases. The cases of abscesses in the intestinal wall caused by *Oxyuris* are also discussed.

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16. Weigmann: Berl. klin. Wchnschr. **58**:732, 1921.
17. Froelich: Rev. mens. d. mal. de l'enf. **15**:497, 1897.
18. Dmitrieff: Zentralbl. f. Chir. **53**:1876, 1926.
19. Hippius and Lewinson: Deutsche med. Wchnschr. **43**:1781, 1907.

TRAUMATIC RUPTURE OF THE HEART

REPORT OF A CASE *

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Spontaneous rupture of the heart associated with some definite existing lesion in the myocardium, such as an infarct, has been frequently observed and reported; likewise, wounds and rupture due to perforation by fractured ribs, bullets and various other types of foreign bodies. On the other hand, rupture due to a more indirect trauma, when the injurious force has been a compression of the chest or abdomen or merely a concussion, while not infrequently described, is still a rather unusual occurrence. However, Cutler and Beck [1] thought that rupture of the heart by contusion occurs more frequently than the reported examples would seem to indicate. The exact nature of the mechanism of this traumatic rupture, however, varies considerably, and would seem frequently to be doubtful. The case to be described is presented, therefore, first, because the lesions differ somewhat from others previously described; and second, because it is thought that the injury may be plainly accounted for by the nature of the mechanical force involved. I should also like to stress the point, in passing, that the medicolegal value of a correct differentiation of traumatic from nontraumatic rupture of the heart on the basis of anatomic observations is plainly very great, and that the not infrequent occurrence of the latter accident should be borne in mind.

REPORT OF CASE

History.—J. B., a white boy, aged 17, on Aug. 13, 1929, while attempting to steal a ride on a truck, slipped off, falling to the ground. A rear wheel of the vehicle passed over his body. He was brought to the accident room of the New Haven Hospital, but was found dead on arrival. Abrasions were found over the upper part of the body, and blood was oozing from the nose and mouth. No family or past history was obtained.

Necropsy.—Necropsy was performed approximately two hours after death. The body was seen to be that of a well nourished white boy, with a well developed bony and muscular structure; the weight was 50 Kg., and the height 162 cm. He did not, however, appear to be as old as his given age. His features were juvenile, hair on his face was scant and there was only a small amount of pubic hair. The external genitalia seemed rather underdeveloped. He was not, however,

* Submitted for publication, Nov. 7, 1929.

* From the Department of Pathology, Yale University School of Medicine.

1. Cutler, E. C., and Beck, C. S.: Surgery of the Heart and Pericardium, Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1927, vol. 4, p. 273.

overobese. There was beginning postmortem rigidity of the extremities and jaws, with a postmortem lividity over the dorsum of the body. The skin showed the following lesions: on the left aspect of the upper lip, there was an abrasion measuring 3 cm. in length and 1.5 cm. in diameter. There were also several other small abrasions and lacerations. A small abrasion was seen on the lower lip and a small cut on its left side measuring 1.5 cm. in length. There were a number of superficial abrasions on the chin. When the buccal mucosa was examined it was seen that the skin and underlying tissues had been stripped away from the mandible for a distance of several centimeters beginning about 2 to 3 cm. from the right of the symphysis, and extending back along the left mandible to a point about half way between the symphysis and the angle. When the skin was reflected downward, it was found that the bone was completely bared by this injury. An ecchymotic area was seen over the right zygoma. Superficial abrasions were seen on the neck, especially the right side, and on the chest, where they took the form of longitudinal striations measuring from 8 to 10 cm. in length. They extended downward and slightly laterally toward the left side of the body. There was also seen a prominence of one of the left ribs, which was evidently broken and projected somewhat beneath the skin, but not through it. On the abdomen, above the left anterior superior iliac spine, there were seen several small blue or purple contusions. Beneath one of these a small, hard mass was felt. On dissection, this was seen to be a small piece of bone, sharp at one end, blunt at the other, measuring 17 by 6 mm. and evidently broken from the ilium, the border of which was irregular. This fragment penetrated the deep fascia and lodged beneath the skin. There was a moderate amount of hemorrhage in the adjacent tissue. On the right knee, just below the patella, there was found an abrasion measuring from 4 to 5 cm. by from 2 to 3 cm. and a smaller one just distal to it. Lymph nodes were felt in the right groin, but nowhere else.

When the peritoneal cavity was opened, there was seen a large quantity of blood, amounting to several liters. The peritoneal surfaces seemed smooth and glistening. The bladder was contracted. The edge of the liver was only a short distance below the costal margin on the right. The blood apparently came from extensive injury to the spleen, which showed a number of deep lacerations. Aside from these, the organ, which weighed 200 Gm., and measured 14 by 8.5 by 2.5 cm., was not remarkable.

When the chest plate was removed, it was seen that each pleural cavity contained several hundred cubic centimeters of blood. The transverse diameter of the heart and pericardium was 10 cm.; that of the chest 24 cm. The pericardial sac was opened in situ and found to contain a small amount of fluid blood. The pericardial surfaces were searched carefully for evidences of injury. None was found laterally, inferiorly or anteriorly. Posteriorly, however, there were found behind the right auricle, openings leading down into each pleural cavity, rather ragged in appearance and measuring from 2 to 4 cm. in diameter. The tears in the pleura reflected over the mediastinum were perhaps somewhat larger. The lateral pleural surfaces seemed intact, smooth and glistening, though there were beneath them a few small areas of hemorrhage associated with fractured ribs, which were as follows: on the right, the second, third and fourth were broken in about the midaxillary line; on the left, the fifth and sixth, slightly more anteriorly.

The heart weighed 205 Gm. It was firm in texture, contracted and evidently contained little or no blood. The pericardial surface was smooth and glistening, except at the apex, posteriorly, where a jagged laceration measuring 1.5 cm. in diameter was found. This lesion was situated in the left ventricle just lateral

to the interventricular septum, and opened directly into the left ventricle. There was also seen to be a small connection through the septum into the right ventricle, just about large enough to admit a probe. There was a rather narrow appearing fissure that led from the main rent laterally and slightly upward, in the left ventricle. Lying free in the pericardial sac was an irregular piece of cardiac tissue. This measured about 3.5 by 1.5 by 0.5 cm. On one small surface was subepicardial fat, which was somewhat torn. On another surface could be seen a small amount of endocardium, and a few fine columnae carneae. The other surfaces showed torn muscle fibers similar to those in the heart lesion itself. This portion of heart wall seemed obviously too small to fill the main opening in the ventricle completely, and seemed more likely to have come from the lateral more fissure-like laceration. No other fragments of cardiac musculature were found lying in the pericardial sac. It is probable that other pieces were torn loose, but were carried with the flow of blood out of the pericardial sac and through the pleural tears, into one of the pleural cavities, where, because of the large amount of blood, they were not observed. There was a small zone of subepicardial hemorrhage just above the rent in the heart, and extensive subepicardial hemorrhage and scattered petechial hemorrhage on the anterior surface of the left ventricle, with blotches of hemorrhage on the lateral surface. The subepicardial fat along the coronary arteries seemed somewhat increased. The arteries were not tortuous, and no obstructions could be demonstrated by probing. When the right side of the heart was opened, the endocardium was found smooth and glistening. Practically no blood was contained within. The foramen ovale was patent, connecting the two auricles by a small channel a few millimeters in diameter, which passed on a slant through the interauricular wall. The tricuspid valve measured 10 cm. in circumference. The valve leaflets were thin and delicate. The chordae tendineae were thin and delicate and attached in their usual position. The columnae carneae and the papillary muscles of the right ventricle were neither flattened nor increased in size. The pulmonic valve measured 5.5 cm. in circumference. The valve cusps were thin and delicate. The myocardium of the right ventricle seemed homogeneous and measured from 3 to 4 mm. in thickness (exclusive of the columnae carneae). When the left side of the heart was opened, it was seen that just above the mitral valve, there was a tear in the endocardium of the auricle, which measured about 4 cm. in length, and which extended down to the musculature, a few of the fibers of which were torn. There was no evident disturbance of the competence of the mitral valve due to this superficial lesion. That valve measured 7 cm. in circumference, the valve leaflets being thin and delicate. The chordae tendineae were also delicate and attached in their usual position. The papillary muscles and the columnae carneae of the left ventricle were not increased in thickness or flattened. The ventricular wall was 12 mm. thick. The aortic valve measured 5 cm. in circumference. The valve cusps were thin and delicate. The aorta above was smooth and flexible, and otherwise not remarkable.

The remainder of the viscera will be described only briefly.

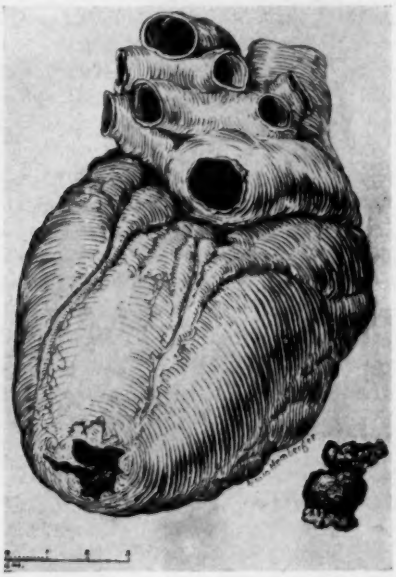
The right lung weighed 375 Gm., the left 275 Gm. Both showed a few small tears in the pleura, a few blebs of interstitial emphysema and blotches of subpleural hemorrhage.

The stomach and duodenum were not remarkable. The pancreas weighed 75 Gm., and measured 16 cm. in length. It was not unusual in appearance. The liver weighed 1,225 Gm., and measured 21.5 by 14.5 by 5.5 cm. The peritoneal surface seemed smooth, glistening and uninjured. At the base of the falciform

ligament, a small amount of extravasated blood was found beneath the capsule of Glisson, due to small, shallow tears in the hepatic substance. Otherwise, the liver was not remarkable.

The suprarenal glands together weighed 5.5 Gm., but showed nothing unusual. The cortex did not seem thinner than usual. The right kidney weighed 100 Gm., and measured 9.5 by 6 by 2.5 cm. The left weighed 125 Gm., and measured 10 by 6 by 2.5 cm. They were essentially normal in all particulars.

The bladder was contracted, and showed no pathologic change. The prostate was small and cut readily. The seminal vesicles were small and contained a small amount of yellow semigelatinous fluid. The testes together weighed 45 Gm. The tunica albuginea was not thickened. The substance was yellow; the tubules did not string out readily when pulled by forceps.



Traumatic rupture of the heart (posterior view). The small drawing shows the portion of the cardiac wall found loose.

The tongue, pharynx, larynx, trachea and esophagus were not unusual, except for numerous small hemorrhagic areas in the mucosa of the larynx and trachea. The thyroid gland weighed 40 Gm., and was not remarkable. The thymus weighed 62 Gm., and extended down over the great vessels. In the connective tissue capsule were some small extravasations of blood. It was light pink externally, and moderately soft. The cut surface appeared more yellow.

In the intestines, there was a well marked hyperplasia of Peyer's patches and of the solitary lymph follicles and of the lymph nodes in the mesentery. The lumen of the appendix was slightly dilated.

The bone-marrow was pink and of the consistency of fluid.

Beneath the scalp over the lower occipital region there was a hematoma measuring 6 cm. in diameter, but relatively thin, and containing only a small amount of blood. No fracture of the skull was found either externally or after removing the vault. In both orbital cavities, a slight amount of extravasated blood was

seen in the orbital fat. Beneath the dura covering the petrous portion of the temporal bone, there were small petechial hemorrhages. The pituitary gland was not unusual. The brain showed nothing of note externally, except a slight flattening of the right hemisphere, probably artefact. Multiple frontal sections revealed nothing of note. The spinal cord was not remarkable either externally or on section.

Microscopic Observations.—Heart: The muscle fibers of both ventricles were not unusual in size or staining properties. A section of the edge of the lacerated region of the apex showed no evidence of unusual cellular infiltrations, and the muscle fibers appeared well preserved. Small extravasations of red blood cells were seen in the tissues adjacent to the torn edge. In scattered areas, likewise, through the left ventricle, small hemorrhages were seen in the connective tissue septums and in the fatty tissue of the epicardium. The fibrous tissue of the heart was not increased, and the blood vessels showed no changes.

Other Organs: A few scattered and clumped red blood cells were seen in the alveoli of the lungs; otherwise, there were no unusual changes. A section through an uninjured area of the spleen showed no changes of note. Postmortem changes were found in the mucosa of the stomach. The other layers were not remarkable.

The pancreas, liver, suprarenal glands, kidneys and bladder presented no microscopic changes of interest.

The alveoli of the prostate were fairly numerous, but small, and the stroma surrounding some of them presented a few scattered small round cells. Spermatogenesis in the tubules of the testes was only moderate with few mature sperms visible.

The structure of the thyroid gland was not remarkable. The lobulation of the thymus was well marked. The cortical and medullary portions were fairly distinct. In the central portion of almost every lobule was seen at least one large, rounded, pink-staining mass, without any definite structure. Hassall's bodies seemed somewhat fewer than usual. Mitotic figures were seen fairly frequently in the medullary portions of the gland.

The aorta was not unusual.

Postmortem changes were present in the mucosa of the ileum. Peyer's patches were hyperplastic with prominent germinal centers, though only moderately numerous mitoses. The lymphoid tissue of the appendix was prominent; the lumen was dilated. The follicular structure of the lymph nodes was seen, but the central portions of the nodes were loosely arranged and rather acellular.

Both the pars nervosa and the pars glandularis of the pituitary gland were well stained and preserved. The arachnoid was somewhat thickened. There was great congestion of the pial vessels and of those of the ependyma of the ventricles. The spinal cord showed nothing of note.

COMMENT

It would seem from the distribution of the injuries in this boy that the wheel of the truck in passing over his body struck first the region of the right shoulder, then passed over his chin, in a glancing manner, thus stripping the soft tissues from the mandible as described. It then rolled on over the chest in a course downward and from right to left and over the left side of the abdomen, severely compressing the chest and abdomen with resulting fracture of several ribs and rupture of the spleen. That more ribs were not broken was undoubtedly due to

the fact that because of youth the chest was flexible, and bent in under the weight of the vehicle, springing back into position after it had passed. The compression was sufficient, apparently, to tear loose a portion of the attachment of the mediastinum, opening channels between the pericardial and the pleural cavities. The passage of the wheel over the great blood vessels prevented the outflow of blood from the pulmonary artery and aorta. The heart was probably dilated from the physical exertion employed in running and attempting to board the truck. As the wheel passed on downward, the blood was forced toward the apex of the heart, and the strain on the musculature was intense. The wall ruptured in that region, which was also the thinnest part of the left ventricle. The force was so great that a portion of the wall was actually blown completely out of the heart as a plug of tissue. The fact that the semilunar valves were not damaged may indicate that the compression acted to force the blood in the aorta and pulmonary artery away from the heart. In regard to the pleural rents, it might be argued that the force of escaping blood from the heart so distended the pericardium that it ruptured with a tearing likewise of the pleurae, allowing the blood to escape thus. On the other hand, it seems more likely that the openings were caused by the distortion accompanying the compression. If the former had been true, it would seem as if there should have been much more extravasation of blood in the mediastinal tissues than was actually present. Cessation of the heart action presumably took place a few seconds or, at most, minutes from the time of the accident, the immediate cause of death being probably exsanguination. This differs from the mechanism in a spontaneous rupture of the heart associated with an infarct, gumma or aneurysm, in which the accumulation of blood in the pericardial sac finally so embarrasses its action that the organ soon ceases to beat. It is conceivable that a traumatic rupture of the heart, less extensive in degree than the one described, might be compatible with life, provided that the rent became filled with clotted blood before too much had been lost. The accumulation in the pericardium would flow off into the pleural sacs, and the heart be thus spared its effect. This fact has been brought forth a number of times in discussions of puncture wounds of the heart and pericardium, in cases in which the patient has survived the accident. In this case, it is obvious that the fractured ribs themselves played no part in the trauma to the heart or even to the pericardium, because of their distance from the lesions.

The relation between the rupture of the heart and the general physical condition is interesting to consider. The underdeveloped sex characteristics seen in this youth and the hyperplasia of thymus and lymphoid tissue are characteristic of so-called status thymicolymphaticus. A weakness and softness of the cardiac musculature are described as occurring

in that condition. It might be felt by some that this played a rôle in the production of the lesion. Even if one were to admit that there is such a definite entity as status lymphaticus, which is questioned by many authorities, it would seem unnecessary to call on that to aid in the explanation of the present case, as the force would seem sufficient to have caused the damage in a sound organ.

Many of the other instances of traumatic rupture of the heart to be found described in medical literature are much less capable of a definite explanation as regards the mode of production than the one here described. Saphir [2] reported the case of a child, aged 4, over whom a motor truck passed with no apparent injury to the chest and but few abrasions on the abdomen. The heart showed a rupture transversely from the midportion of the anterior surface of the left ventricle, across the left margin ending in the lower third of the posterior surface of the left ventricle near the interventricular septum. The tear measured about 6.5 cm. in length. Microscopically, the cardiac musculature showed no degeneration, fibrosis or inflammatory reaction. The right pubic and iliac bones were the seats of fractures with hemorrhage into the adjoining fascia and the peritoneal cavity. In this child, the thymus weighed 30 Gm., and the mediastinal, peritoneal and retroperitoenal lymph nodes were enlarged. The aorta, however, showed no hypoplasia. He felt that a status lymphaticus was not present despite these appearances. His explanation of the rupture was that it was due to trauma with the greatest force acting in the region of the right pelvis. He did not explain how this force actually produced the lesion, and he stated that spontaneous rupture could not be absolutely excluded. Turner and Gould [3] described an accident in which a 47 year old sailor fell a distance of 20 feet (6 meters) apparently landing on his head. He lived five hours after entrance into the hospital. Aside from a few superficial bruises and lacerations on the face, scalp and hips, the only gross injury to the body was a fracture of the first segment of the gladiolus. There was no tear in the parietal pericardium. A small extravasation of blood was seen in the anterior mediastinum and about 450 cc. of blood in the pericardial sac. The right side of the heart was collapsed. The cardiac musculature appeared normal and healthy, aside from a small tear found in the anterior wall of the right ventricle close to the semilunar valves, large enough to admit a lead pencil into the ventricular cavity. They thought that the fracture of the sternum was due to indirect violence, the result of sudden flexure of the spine, with an accompanying pressure on the heart, and the production of a small

2. Saphir, O.: Rupture of the Heart by Indirect Trauma in a Four Year Old Boy, Am. J. M. Sc. **173**:353, 1927.

3. Turner, G. R., and Gould, L. P.: A Case of Traumatic Rupture of the Heart, Lancet **2**:567, 1917.

opening. From the clinical observations, they felt that there was an initital slight hematopericardium, with the formation of a clot in the opening. This later dislodged and the sudden distention of the pericardium with blood caused death. A case reported by Howat [4] is somewhat similar. A healthy shipwright, aged 23, fell 45 feet (14 meters) landing on some wooden planks and steel plates. He was found dead on his arrival at the hospital, twenty minutes later. A few scratches and bruises were found at the right elbow, but no other gross external injuries. Lacerations were found in the liver with fluid blood in the peritoneal cavity and an extravasation into the retroperitoneal tissue from lacerations of the right kidney. Blood was also seen in the loose tissue of the posterior mediastinum. The pericardium was intact, with about 750 cc. of blood contained within the sac. A slitlike opening was found leading into the cavity of the left auricle, situated exactly in the free edge of the auricular appendage, and measuring about 0.25 cm. in length. Microscopic sections showed no cardiac disease. Howat felt that traumatic rupture of the heart within an intact pericardium is almost certainly due either to compression or to concussion. The former may act either by directly bruising the heart tissue so that the injured part gives way immediately, or later, or else without this direct injury, by so increasing the intracardiac blood pressure that the healthy heart wall is burst from within. In this particular instance, he felt that the blood pressure increase on a distended auricle was such as to drive the contained blood away from the natural orifices toward the blind extremity of the auricular appendage. The part played by concussion here is not certain. He cited another instance of a 68 year old brick layer who had his chest compressed, dying five weeks later with a rupture of the heart near the apex through a bruised area, of which there were several. No other cardiac lesion was found. He thought that this is an example of the delayed effect of traumatic injury of the heart. Traumatic rupture of the heart with uninjured chest wall was reported by Kellert,[5] who said that a 44 year old Italian workman was caught in a cave-in of a sand bank and buried to his waist. He was dead when dug out. The autopsy was performed eight days later on the embalmed body. Over the anterior aspect of the chest, especially on the left, were five small abrasions, while below both knees were likewise abrasions. No fractures were in evidence. The peritoneal cavity contained approximately 1 liter (1,000 cc.) of bloody formaldehyde-containing fluid. The left pleural cavity contained a large amount of fluid, and clotted blood, 1,800 cc. in all, with a compression of the lung into the upper portion of the cavity. In the pericardium was a large amount of firm blood clot

4. Howat, R. K.: Traumatic Rupture of the Heart, Lancet **1**:1313, 1920.

5. Kellert, E.: Traumatic Rupture of the Heart: Report of a Case with Uninjured Chest Wall, J. Lab. & Clin. Med. **2**:726, 1917.

surrounding the heart and adherent to the pericardial surfaces. The lower left portion of the pericardial sac presented a ragged opening, 4 cm. in diameter, which was filled with firm, friable blood clot, and communicated with the left pleural cavity. The heart weighed 370 Gm. Near the apex on the right posterior surface was a ragged linear laceration of the heart wall measuring 5 cm. in length, communicating with both ventricles, the laceration extending across the interventricular septum. Just beneath the right auricle were two minute openings in the fat and myocardium. In the left ventricular wall beneath the auricular appendage was a transverse laceration in the heart muscle, 2.5 cm. long. The papillary muscles of the right ventricle were lacerated, the portion attached to the chordae tendineae being found free in the auricle. The endocardium of the auricle above the tricuspid valve was lacerated. The papillary muscles of the left ventricle were likewise torn from their attachment to the cardiac wall. The aorta at its origin was separated through one half of its circumference. Microscopically, there was a slight amount of fatty infiltration of the right ventricular wall and vacuolization in the muscle fibers with increased amount of pigment about the nuclei, which varied greatly in size. An occasional area of fibrosis and a rare focal accumulation of lymphocytes, endothelial cells and polymorphonuclear leukocytes were seen. Kellert suggested two possibilities to explain the origin of the lesions. One is that the weight of the falling earth, which was soft and compressible, caused equal pressure over the chest resulting in great compression and bursting of the heart, much as though a rubber bag distended with fluid were compressed at its middle. He thought, however, that such an effect without fracture of the sternum or ribs was unlikely. The second explanation, which he felt was more probable, is that the large quantity of sand around the lower part of the body exerted such pressure that most of the blood was driven out of the vessels with a resulting overdistention of the heart and multiple rupture. It was his opinion that the ruptured pericardium was an indication of the greatness of the intracardiac force, and that the pathologic changes in the heart, though slight, probably contributed to the severity of the injury.

Kellert quoted a number of other articles describing traumatic rupture of the heart. One is described by DuFour,[6] in which a 13 year old girl underwent severe compression of the thorax and strangulation. There was no wound of the chest wall or pericardium, but a rupture of the right auricle. McOscar and Voelcher[7] cited the case of a man

6. DuFour: Rupture de l'oreillette droit par compression du thorax combinée avec la strangulation a l'aide des mains, Ann. d'hyg. **16**:185, 1911.

7. McOscar, J., and Voelcher, A.: On a Case of Traumatic Rupture of the Interventricular Septum, Tr. Path. Soc. London **48**:47, 1896-1897.

who died eight days after being run over by a wagon. No fractures of ribs or sternum were found, but a transverse rupture of the ventricular septum 2.5 cm. in length. O'Neill [8] reported a boy 9 years old who was knocked down and jumped on by other boys. He walked home, but died at the end of eight days. A hematopericardium was found and a small rupture at the auriculoventricular junction of the left side of the heart. No wounds of the chest were mentioned. The case of a man, aged 44, who was struck by a heavy weight and died forty-two hours later, was cited by Kugel.[9] A hematopericardium and a sharp tear in the right ventricle were found. The heart was enlarged, and fatty masses were present on the surfaces of both ventricles. No fractures were present. Robertson [10] gave the case of a 49 year old man who fell from a railroad carriage, hitting his left shoulder on the ground. Death occurred forty-five minutes later. No wounds of the chest were present. The pericardium was intact, but there was a rent 3.1 cm. long in the left ventricle. Gibbons [11] told of a coolie who died three hours after being struck over the chest and elsewhere by a bamboo stick. No penetrating wounds were present. The heart, however, presented a rupture at the apex communicating with the right ventricle. Hutchinson [12] described a rupture of the right ventricle caused by a kick on the chest from a horse. The man died fourteen hours after the injury. There was no break in the skin of the chest. A tear in the pericardium anteriorly and a rupture at the apex of the right ventricle were revealed by necropsy. Groom [13] wrote of a boy, aged 16, who was caught between the shaft of a pony cart and a wooden railing. Death took place one month later. A rupture 2.5 cm. long in the posterior portion of the left ventricular wall in an aneurysmal dilatation was found at necropsy. The trauma probably weakened the wall of the heart, allowing the production of the aneurysm, which later broke. Peacock [14] gave the story of an athlete, 25 years of age, who was struck a blow in the epigastrium, and died forty minutes later, a laceration 8.75 cm. long being found in the right ventricle.

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8. O'Neill, B. J.: A Case of Traumatic Rupture of the Heart, J. A. M. A. **62**:697 (Feb. 28) 1914.

9. Kugel, A.: Ein Fall von Herzruptur, Prag. med. Wchnschr. **34**:303, 1909.

10. Robertson, C.: Note on a Case of Rupture of the Heart, Lancet **1**:240, 1897.

11. Gibbons, J. B.: Rupture of the Heart by a Blow with a Stick: Survival for Over Three Hours, Indian M. Gaz. **32**:443, 1897.

12. Hutchinson, F.: Case of Traumatic Rupture of the Heart, Brit. M. J. **2**:1427, 1894.

13. Groom, W.: A Case of Rupture of the Heart, Lancet **1**:1202, 1897.

14. Peacock, T. B.: Case of Rupture of the Right Ventricle of the Heart, Tr. Path. Soc. London **31**:72, 1880.

There have been still other reports of traumatic cardiac rupture, among which is that of Godlee,[15] who mentioned a case of rupture of the right ventricle likewise caused by a blow of the fist, in this instance, on the precordium. Stephens[16] cited the case of a healthy boy, aged 16, who suffered a compression of his abdomen and chest by a heavy steel tube which was being lowered by a crane. He stepped back a few paces and fell dead. Postmortem examination showed a pericardial sac full of blood and a tear 2.5 cm. long in the right ventricle. Stephens raised the question as to whether this was produced by the back pressure caused by the tube against the abdomen. Bilderbeck[17] reported the instance of a soldier, 19 years old, who was caught between the cross-bar handle of a wheeled fire pump and a stone wall. The blow struck him across the middle of the chest. He was seen to fall dead at once. Postmortem examination showed some slight contusions and cuts about the head, but no fractures or other serious external lesions. The ribs were pliable, so that it appeared as if the chest could be easily compressed. The pericardium was full of blood, but undamaged. The heart was small, and the valves and musculature were apparently normal with no trace of old disease process. In the right auricular wall between the right coronary artery and the entrance of the inferior vena cava was a small rent measuring about 1.9 by 1.25 cm. Bilderbeck believed that at the moment of the accident, the man took a deep inspiration, engorging the right auricle, which then burst on the sudden compression of the costal wall. Kennedy[18] reported the case of a woman between 60 and 70 years of age, who was knocked down by a cart, dying about one hour later. No bruises were found externally, but several ribs were found broken, as well as the sternum, though the parietal pericardium was not injured. About 300 cc. of blood was contained within the sac. In the anterior wall of the left ventricle, there were two ruptures half an inch apart extending across the wall a short distance below the auriculoventricular groove. The upper wound measured 3.75 cm. on its epicardial surface, but on its endocardial surface only about 1.7 cm. The lower wound was 1.25 cm. long. Both were ragged. The heart musculature was soft and pale, and microscopically there was some brown atrophy, but not excessive for her age. Kennedy felt that in view of the small amount of coronary disease and the character of the wounds, the mechanism of production of the lesions was rupture by bursting.

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15. Godlee, R. J.: The Repair of Wounds of the Pericardium and Heart, Oxford Surgery **4**:173, 1918.

16. Stephens, G. A.: Three Thoracic Emergencies, Lancet **2**:1382, 1922.

17. Bilderbeck, A. C. S.: Traumatic Rupture of the Heart without Fracture or External Lesions, Brit. M. J. **1**:675, 1919.

18. Kennedy, A. M.: Rupture of the Heart by External Violence, Lancet **7**:105, 1914.

Heger-Houbotte [19] described two cases, the first of a man who fell 30 meters sustaining only rather superficial external lesions, but a fracture of three ribs. There was an extensive rent in the right auricle and ventricle and the septums between the right and left sides of the heart. He thought that the fracture of the ribs could explain the ruptures. The second case was that of a chauffeur who was thrown violently from a car, dying instantly. The external lesions were not significant. The right ventricle showed a star-shaped wound near the tip on the posterior surface. He felt that the heart was forced against the vertebral column and the ventricle ruptured from the pressure of the blood.

Schütt [20] cited an accident in which a 41 year old man suffered a marked compression of the chest between two heavily laden automobiles and died immediately. External wounds were slight. Fractures of several ribs were found anteriorly near the sternum and posteriorly near the vertebral column. The pericardial sac contained about 250 cc. of blood, for the most part fluid. A few hemorrhagic areas were seen in the mediastinum. A tear, 20 cm. long, was present in the pericardium near the junction of the mediastinum and diaphragm. The heart showed extensive tears, in the right ventricle, pulmonary artery, aorta and left ventricle, with ecchymotic areas on the posterior aspect of the latter. It was Schütt's opinion that the force acted from the region of the right shoulder downward and posteriorly causing the fracture of the ribs and exerting a downward pull on the heart, tearing the pulmonary artery and aorta and causing the wounds in the heart itself, ripping the pericardium and bruising the posterior aspect of the left ventricle against the vertebral column. He stated that cases of traumatic rupture of the heart can be grouped into those with a bursting rupture (Platzruptur) and those with a rupture due to a twist (Zerrungsruptur). He quoted Jaffé [21] to the effect that the former is due to an explosive action through hydraulic pressure, while the latter is associated with a compression or distortion which causes a tear in the region most severely pressed on.

CONCLUSIONS

This case differs from the cases reported in the literature reviewed, inasmuch as it is the only one in which the actual extrusion of a portion of cardiac wall was observed. The latter fact would seem to be strong evidence of a bursting due to increased intracardiac pressure.

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19. Heger-Houbotte, M.: Rupture traumatique du coeur, Arch. internat. de méd. lég. **2**:292, 1912.

20. Schütt, W.: Ueber einen Fall von Traumatischer Herzruptur nach Brustquetschung, Centralbl. f. allg. Path. u. path. Anat. **31**:169, 1920.

21. Jaffé, R.: Sprengung des linken Ventrikels durch Pufferverletzung, München. med. Wchnschr. **64**:742, 1917.

In this instance, likewise, the manner of application of the force producing the lesion seems evident. It many of the other instances described in the literature, the trauma was more indirect, and one often wonders just how the damage was brought about. Cutler and Beck,[1] who were quoted at the beginning of this article, felt that the mechanism of contrecoup may play a part, but the compressibility of the thoracic wall, combined with the toughness of the pericardium as compared with the friability of the cardiac muscle, makes it evident that the heart may be damaged without a tear in the pericardium. That a great increase of intracardiac pressure may produce a rupture of an apparently healthy heart would seem true. Whether or not sufficient pressure can be caused by forcing the blood from the lower extremities and perhaps partially from the abdominal viscera as suggested by Kellert is difficult to decide. Animal experimentation might help solve the problem. The effect of concussion in producing ruptures of the liver, spleen and mesentery has frequently been observed and discussed, and it does not seem illogical to suppose that the effect on the heart might be the same. In several of the cases, reports of which have been cited here, there was some indication that the myocardium had suffered some previous, unrelated damage, which undoubtedly was a contributing factor in the production and extent of the injury to the hearts. Strong advocates of status thymicolymphaticus might hold that in the instance here described, there was a predisposing factor of weakness of the cardiac musculature. It is difficult either to deny or to prove this.

I draw the conclusions from my case and others reported that traumatic rupture of the heart may be brought about by (1) great increase of intracardiac pressure; (2) concussion or direct compression acting on the heart to cause immediate tears, or bruises which later give rise to perforations.

MYCOTIC ANEURYSM OF THE SUPERIOR MESENTERIC ARTERY COMPLICATING BACTERIAL ENDOCARDITIS

REPORT OF THREE CASES *

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Mycotic aneurysm is a relatively infrequent complication of bacterial endocarditis. A lesion of this type involving the superior mesenteric artery and its branches has been reported in but twenty-five of all the case reports which have been compiled. Localization in the superior mesenteric artery is considered by Aschoff [1] to be next in infrequency to that in the coronary artery. Von Schrötter [2] found only one instance of involvement of this vessel in 19,300 autopsies. Leaflet and aortic lesions are the most frequently reported, and multiple aneurysms have been encountered on a few occasions.

Since we are discussing only those aneurysms of which intravascular bacterial infection is the cause, only the theories in regard to the production of this type of lesion will be considered. The most frequent predisposing factor in the formation of these lesions is bacterial endocarditis, although septicemia, from any cause, may be the source.

Stengel and Wolferth [3] mentioned three methods by which the process develops: (1) lodgment of infected emboli in the lumina of the vessels, or vasa vasorum; (2) the settling of bacteria on the inner surface of the vessel or vasa vasorum (this being the case only in the heart and aorta), and (3) by the continuity, or contiguity, of infection of the aortic or pulmonic valve.

In the mesenteric artery, most of the aneurysms are doubtless embolic, and in vessels of this caliber they are probably due to infected

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1. Aschoff, cited by Kolin, L.: Zur Kenntnis der Anatomie, Klinik und Therapie des Aneurysma der Arteriae mesentericae superioris, Arch. f. klin. Chir. **123**:684 (March) 1923.

2. Von Schrötter: Erkrankung der Gefässe, in Nothnagel's spezielle Pathologie und Therapie,, 1901, vol. 15, p. 271.

3. Stengel and Wolferth: Mycotic Aneurysms of Intravascular Origin, Arch. Int. Med. **31**:527 (April) 1923.

material being held in contact with the vascular intima by angulation, bifurcation or immediate narrowing.

Eppinger [4] was of the opinion that the infection is set up first in the adventitia, and involves the media and intima secondarily. However, Benda,[4] Unger [4] and many others felt that the process is primarily an endothelial injury, with subsequent involvement of the other coats, and explained the progress of the lesion as follows: With the contact of infected material and subsequent endothelial necrosis, the wall becomes progressively involved; pressure pounding on this weak surface produces dilatation and subsequent outpouching of the vessel wall.

Klotz has shown that both intima and adventitia may be involved at the same time, the former through the lodgment of the septic emboli in the lumen, the latter through bacterial embolism in a devitalized wall through the vasa vasorum.

Microscopic study of the aneurysms in our cases shows that they were probably produced in the manner explained by Benda [4] and Unger.[4]

REPORT OF CASE

CASE 1.—*History.*—A 16 year old boy had been sick for a week with soreness and pain in the abdomen, which was worse around the umbilicus, when first noticed, but at the time of examination was most severe in the right lower quadrant. The initial attack came on after the patient had eaten breakfast, and was accompanied by twenty-four hours of vomiting and bloody mucous in the stools. The patient's past history revealed that he had had diphtheria when he was 4 years old, and acute inflammatory rheumatism when he was 9. During the latter illness, "almost every joint in his body" was involved at some time. He had a tonsillectomy one year previous to entry, because of numerous attacks of tonsillitis. Not long after this, he noticed that he was tired and worn out all the time, and was told by a physician that he had heart disease. A few months later, he had an attack of acute abdominal pain in the left side, which remained "sore" up to the time he entered the hospital. He had had some dyspnea on exertion, but not palpitation or edema.

Physical Examination.—On examination, he appeared pale and sick. The heart was markedly enlarged. The left base extended to the axillary line and the point of maximum impulse was in the fifth interspace and about one-half inch (1.27 cm.) outside the midclavicular line. Both a systolic murmur and a diastolic murmur were present; the latter was loud and heard over the aortic area. The abdomen was tense and tender, and rigid over the right rectus muscle. There was slight clubbing of the fingers. The urine was loaded with bacteria, pus and albumin. The red blood cell count and the hemoglobin content were essentially normal, but there was a leukocytosis of 32,000, 84 per cent of the cells being polymorphonuclear neutrophils.

Course.—Vomiting persisted intermittently throughout the entire course of the illness. One week after admission, the patient had sixteen clonic convulsions in twenty-four hours, and a firm, tender, pulsating mass was felt in the upper left epigastric region.

4. Eppinger, Benda, Unger, Klotz, cited by Stengel and Wolferth (footnote 3).

Necropsy (by Dr. Watson Campbell).—Some blood-tinged fluid was seen in the peritoneal cavity. A massive retroperitoneal hemorrhage originating in an eroded hemorrhagic infarct near the pelvis of the right kidney was encountered. This had almost completely decapsulated the kidney. There was a large mass, the size of an orange, in the mesentery, which was found to be a mycotic aneurysm of the superior mesenteric artery. It was filled with a laminated thrombus. Infarcts were found in the spleen and the kidneys. There were large and small vegetations on the mitral valve. Just below the aortic valve, on the mural endocardium, there was a large vegetation.

A large mycotic aneurysm of the superior mesenteric artery with laminated thrombus (case 1). A probe is seen in the lumen of the artery leading into the aneurysmal sac.

CASE 2.—*History.*—A white man, 41 years old, who had been ill for three months, complained of weakness, night sweats and fever. He had lost 45 pounds (20.4 Kg.) in weight, and was having frequent attacks of pain throughout the abdomen, particularly under the left costal margin. The patient's past history was negative for rheumatic fever, infectious diseases of childhood and focal infection.

Physical Examination.—On examination, the patient was pale and anemic. His temperature was 102.8 F. (39.4 C.); pulse rate, 120, and blood pressure,

132 systolic and 86 diastolic. His heart was slightly enlarged, and extended 12 cm. to the left of the midsternal line. There was rather marked heaving of the apex in the fifth interspace, 2 cm. outside the midclavicular line. A loud blowing systolic murmur could be heard over the entire precordium, more marked over the apex. The abdomen was tender and rigid over the right rectus from the costal margin to the pubis, most marked in the region of the umbilicus. There were 3,680,000 red blood cells, and 12,000 leukocytes. The hemoglobin content was 65 per cent. Small quantities of albumin and occasional red cells and casts were found in the urine. A pure growth of *Streptococcus viridens* was isolated from the blood.

Course.—The patient grew progressively worse and four months after the first examination began to show petechiae in the conjunctiva and buccal mucosa. The attacks of pain in the abdomen and splenic region became an almost daily occurrence, and during the last month of his life he suffered blindness of one eye, with severe headache, and a few days later a slow progressive hemiplegia, and died.

Comment.—One interesting feature about this case was the fact that several times after a severe attack of abdominal pain, obviously due to emboli in the visceral vessels, the patient would have the typical symptoms and the physical appearances of intestinal obstruction, which would clear up after from twenty-four to forty-eight hours.

Necropsy.—Anemia and emaciation were marked. Petechiae were scattered diffusely over the entire skin and in all the visible mucous membranes. The heart weighed 272 Gm. and was flabby. The mitral valve was encrusted with large fresh vegetations, which extended up onto the auricular wall and involved the mitral leaflet of the aortic valve. Small vegetations were present on the corpus arantii of each aortic cusp. The spleen and the kidneys were peppered with white infarcts of varying size. Many were healed, and in the spleen some of these infarcts had undergone abscess formation. There was a small, round mass in the mesentery, to which was attached a Meckel's diverticulum. On careful examination, this mass was found to be a small mycotic aneurysm of one of the branches of the superior mesenteric artery. It measured 25 mm. in diameter and on cross section was completely filled with a typical laminated thrombus.

CASE 3.—*History.*—A woman, 38 years old, was suddenly stricken with numbness in the feet and legs, and was unable to walk for an hour. Three months later, she presented dyspnea on exertion, swelling of the feet and ankles, and pain over the left kidney. She lost 25 pounds (11.3 Kg.) in weight.

Physical Examination.—On examination, seven months after the onset of the illness, the patient was anemic and emaciated, and there was impairment of vision in the right eye. The conjunctivae were dotted with petechial hemorrhages. The heart was of about normal size. A loud systolic murmur was heard over the apex, and was transmitted to the axilla. Examination of the upper part of the abdomen was unsatisfactory because of marked tenderness and rigidity in the right hypochondriac region. There was marked tenderness over the area of the right kidney. The spleen could not be felt. The feet and the ankles were edematous. *Streptococcus viridans* was obtained repeatedly in blood cultures. The urine contained a large amount of pus and red cells on all examinations. The leukocyte count was 21,600. There was marked secondary anemia that grew progressively worse.

Course.—One week after admission, the patient presented marked edema of the feet and legs and subsequently, all the symptoms and observations of severe cardiac failure. She died four weeks after admission.

Necropsy.—Marked anemia was present, and petechial hemorrhages were found in the conjunctiva and in the skin over the knees. The spleen contained many anemic infarcts, some showing abscess formation. The kidneys were riddled with variable-sized healed and anemic infarcts, and there was an acute hemorrhagic nephritis superimposed. A large mycotic aneurysm of the superior mesenteric artery, measuring 9 by 5.5 by 5 cm., was found in the mesentery. It was partially filled with a laminated thrombus and red clots, and its walls were as much as 12 mm. thick. The heart weighed 275 Gm., and the mitral valve was covered with thick vegetations and the leaflets were badly ulcerated. These vegetations had extended as far as 3.5 cm. on the mural endocardium of the left auricle, and down onto the chorda tendineae of the mitral leaflets. Other observations were of no particular interest.

CLINICAL COMMENT

In view of the fact that in most cases bacterial endocarditis demonstrates embolic phenomena for months before death, it is surprising that mycotic aneurysms of the mesenteric vessels are not far more prevalent than one would be led to believe from a review of the literature.

However, since in many cases the aneurysm is small and the lumen well filled with a laminated thrombus so that pulsation is slight (as in our case 2) and rigidity and tenderness make abdominal examination unsatisfactory, it is not surprising that so few cases can be diagnosed clinically.

The patient in case 1 lived for six weeks during the development of the tumor; on finding a movable pulsating mass not connected with the aorta, Dr. Campbell made the clinical diagnosis of mycotic aneurysm of the mesenteric artery.

In cases 1 and 2 an attack of abdominal pain, followed by nausea and vomiting, rigidity and tenderness, distention and obstipation marked the onset of the trouble. In case 3, there were no symptoms referable to abdominal pathologic conditions, and though this tumor was almost as large as an orange, the finding of it was entirely a matter of post-mortem enlightenment, as the finding of most of these aneurysms is.

The rapidity with which the tumor develops is, of course, largely dependent on the surrounding structures and the amount of pressure that is placed on the weakened surface of the blood vessel. As can be seen from an examination of the clinical histories in these cases, two of the aneurysms in the main stem of the mesenteric artery developed into remarkably large tumors in the short period of from three to five weeks, while the aneurysm in case 2 was small, and as nearly as could be determined from the history, had apparently been developing twice as long as those in the other cases.

The erosive nature of these lesions naturally predisposes the blood vessel to rupture, but this complication was not encountered in this small series.

Although intracranial aneurysm of this type was not diagnosed clinically, it should have been suspected in case 2 because of the slowly progressing neurologic symptoms. However, a differentiation from embolism with thrombus formation would have been largely speculative. Unfortunately, no autopsy on the brain could be obtained.

It is interesting to note that, although small vegetations were continuously being carried away from the leaflets by the vascular circulation in these cases, not one showed multiple aneurysms. This fact merely bears out the known contention that the endothelium of the vascular system is resistant; in all probability infection can get a foothold only when the nature of the vessel is such that the infected emboli are held in contact with the wall over a period of time. Several times, in case 2, emboli lodged in the superficial vessels, causing marked tenderness, severe pain and swelling, but on each occasion the processes subsided after three or four days. One particularly painful lesion was in the palm of the right hand, but this, like the others, cleared up in about a week.

CONCLUSIONS

Three cases of mycotic aneurysm of the superior mesenteric artery complicating bacterial endocarditis are reported. Only one was diagnosed clinically. None of these aneurysms ruptured. Multiple lesions were not found. The finding of three cases in a small series suggests that they are frequently overlooked.

PRIMARY SQUAMOUS CELL CARCINOMA OF THE VAGINA COMPLICATING LATE PREGNANCY IN A PATIENT SIXTEEN YEARS OLD*

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The case here reported is described because it illustrates the occurrence of a tumor which is uncommon in an extremely youthful person and which is a rather rare complication of pregnancy.

REPORT OF CASE

The patient, a negress, aged 16, was admitted to the wards of the Northwestern General Hospital, in the service of Dr. Van Dolsen, Dec. 28, 1928, on account of vaginal bleeding, abdominal enlargement, leukorrhea and abdominal pain. The last menstrual period had begun on May 25, 1928; since then, the abdomen had become progressively larger. In the latter part of November, 1928, the patient began to pass blood in the form of clots from the vagina; this continued until the time of admission. She had lost about 20 pounds (9 Kg.) since October; otherwise, her history was unimportant. Prior to admission, she had been a patient in another hospital, where her symptoms had been diagnosed as due to fibroid tumor. The patient was married in July, 1928, but admitted that she had had sexual relations at least two years previously. She said that intercourse was never painful, and that slight leukorrhea had been present as long as she could remember.

Examination on admission showed a moderately well nourished young woman. The results of the examination were essentially negative, except for the external signs of pregnancy and the enlargement of the uterus to a point above the umbilicus. On vaginal examination, a cauliflower-like growth was seen and felt involving the upper two thirds of the posterior vaginal wall, extending to the posterior culdesac, but not invading either the cervix or the anterior vaginal wall. The cervix was soft and admitted one finger. There was some involvement of the anterior wall of the rectum, but as yet no breaking through of the mucosa. The growth was friable and bled easily. The urine on admission showed from 1 to 2 red blood cells per high power field, and from 3 to 5 white blood cells per high power field. These cells increased markedly in number as the condition progressed. The blood count showed: hemoglobin, 74 per cent; red blood cells, 4,020,000; white blood cells, 16,650; polymorphonuclears, 87 per cent; small lymphocytes, 12 per cent, and eosinophils, 1 per cent. Both the Kolmer and the Kahn serologic tests for syphilis were negative. The values of blood sugar and urea were normal.

On December 22, a biopsy was done, a small portion of the growth being examined histologically (see accompanying photomicrograph) and reported on as follows: Section showed large numbers of islands or nests of squamous epithelial

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* From the Laboratories of the Northwestern General Hospital.
* Read before the Philadelphia Pathological Society, Oct. 10, 1929.

cells, growing in and invading, in an irregular fashion, a stroma consisting of fibrous connective tissue and containing large numbers of small round cells, plasma cells and a few polymorphonuclear leukocytes. The tumor cells showed only a slight tendency to differentiation, with the formation of epithelial pearls. The nuclei of these cells were large and hyperchromatic and showed numerous mitoses. A diagnosis of squamous cell carcinoma was made. The source of this tumor, from the history, could only be the squamous epithelium of either the vagina or the cervix. Since the latter was free, it must have arisen primarily from the vagina.

Section of primary squamous cell carcinoma of the vagina.

On Dec. 26, 1928, 30 mg. of radium was implanted by means of needles into the mass on the posterior vaginal wall. Following this implantation, bleeding lessened considerably. On December 29, because the child seemed viable, a cesarean section was done by Dr. Van Dolsen, and he delivered a living male child that died shortly after delivery. At the time of operation, the cervix was palpated vaginally and found to be hard and rigid, but not involved by the carcinomatous mass. Following the operation, the patient's course was progressively down hill, with marked emaciation, an irregular temperature ranging between 100 and 103 F., rapid pulse, increasing anemia and a progressively increasing leukocytosis, the total leukocyte count just prior to death being 94,500 with 98 per cent polymorphonuclears. On Jan. 30, 1929, an enlarged right inguinal gland was removed. On histologic examination, it showed metastatic squamous cell carcinoma, the section presenting numerous epithelial pearls. On Feb. 3, 1929, a rectovaginal fistula developed; the

condition grew worse and the patient died, Feb. 9, 1929. Permission for an autopsy unfortunately could not be obtained. Vaginal examination at the time of death showed the presence of the rectovaginal fistula; the tumor was felt as a flat infiltration of the remaining posterior vaginal wall. The cervix was apparently still free. A small portion of the tumor was removed from the rectum posteriorly for section. Histologically it showed invasion of the rectal wall down to the mucosa by tumor cells.

COMMENT

Primary squamous cell or epidermoid carcinoma of the vagina is a comparatively rare condition, making up about 0.43 per cent of all carcinomas of women and from 0.26 to 3 per cent of carcinomas involving the female reproductive organs. Among the possible exciting factors, the irritation caused by pessaries receives frequent mention in the literature, but as Williams [1] pointed out, the irritation theory is not strongly supported, since the vagina is more subject to all kinds of irritation than other organs; moreover, vaginal prolapse and invagination, conditions of maximum irritation, are seldom accompanied by cancer. The proportion of cases secondary to the use of the pessary is extremely small in comparison to the enormous number of instances in which the pessary is used. Certainly, in the case just described, this factor could be excluded. Several cases have been reported of carcinoma developing on the site of epithelial hyperplasias, such as leukoplakia, ichthyosis or kraurosis, but these conditions usually occur in women of advanced years.

Embryologically, the vagina is derived from the lower end of the wolffian ducts, the cells of which are of epiblastic derivation. It is possible that during the process of development of papillary structures like the vaginal mucosa, some epidermoid cells may become detached and form rests from which carcinoma may develop. If one assumes that these rests exist, the possiblity then suggests itself that in the case in question the marked proliferation of tissue accompanying pregnancy might have served as a stimulus to such epithelial rests and thus predisposed them to the formation of cancer. The exact influence of pregnancy as an exciting factor in the production of cancer is not known; conflicting opinions exist, but the majority favor the idea that, once established, carcinomatous lesions seem to grow more rapidly with the advent or in the presence of pregnancy, possibly because of the increased nutrition and vascularization of the tissues. Search of the literature failed to find any information or data concerning the influence of pregnancy in the production of carcinoma, provided, of course, that the soil is fertile.

The onset of the vaginal bleeding, which was the first symptom the patient complained of, occurred late in the fifth month of pregnancy,

1. Williams: New York M. Rec. **60**:841, 1901.

and death occurred in less than three months from this time. It seems hardly likely that the tumor could have been present for more than five months without giving rise to any symptoms, and one can assume, therefore, that the tumor must have grown after the onset of pregnancy rather than before it.

The course of these tumors is usually rapid, the shortest time from the onset of the initial symptoms in Williams' series being eight months, the longest twenty-six and five-tenths months and the average sixteen and five-tenths months. The total duration of the disease from the time of the initial symptoms in this patient was less than three months; it is not unlikely, however, that the operative procedure served to shorten the patient's life materially.

Another unusual feature in this case was the age of the patient, she being unusually young not only for carcinomatous tumors in general, but particularly for carcinoma of the vagina. The usual age for this tumor, according to Williams' statistics, is that between 50 and 60 years, which is a little older than that for carcinoma of the cervix. Williams' youngest patient was 17 years old; he regarded reputed examples of vaginal cancer occurring at earlier ages with suspicion; this applied especially to the oft-cited cases in a child aged 3½ and in a girl aged 9, described by Guersant and by Johannorsky, respectively, in which the disease was evidently sarcomatous.

Although the tumor is seldom seen in its early stages, according to Pozzi [2] it occurs initially in one of two forms—either as a papillary growth in the form of single or multiple warts or as a nodular or infiltrative form. In the more advanced stage, cauliflower, villous, highly vascular and more frequently ulcerative types are seen. The usual location is on the posterior vaginal wall, most frequently in its upper segment. From here the disease usually spreads backward to the rectum with symptoms of obstruction and eventual formation of a rectovaginal fistula, as occurred in this case. Spread of the disease to the adjacent lymph glands of the iliopelvic group and particularly both inguinal groups is usually a late manifestation. Dissemination to the internal organs or distant parts is uncommon, death usually occurring before this from either progressive cachexia or, not uncommonly, peritonitis.

Histologically, the tumor presents the usual features of squamous cell carcinoma, except that pearl formation and cornification are not prominent.

SUMMARY

A case of primary squamous cell carcinoma of the vagina, an uncommon type of tumor, is reported as a rather unusual complication of late

2. Pozzi: Quoted by H. S. Crossen: Diseases of Women, ed. 5, St. Louis, 1922, p. 314.

pregnancy in a girl of 16. The onset of the vaginal bleeding, which was the initial symptom, occurred late in the fifth month of pregnancy, making it likely that the formation of a tumor occurred after the onset of the pregnancy, rather than before it. Because of the extreme youth of the patient, the predisposing factors usually mentioned, namely, pessaries and epithelial hyperplasia such as kraurosis, can be excluded. It is therefore suggested that the origin of the tumor might have been in epithelial rests of the wolffian ducts, these rests being stimulated to the production of cancer by the proliferative changes of early pregnancy. The course of the disease in this case was much shorter than in any of the previously reported cases, death from marked cachexia occurring in less than three months from the time of the appearance of the initial symptom.

I. EXPERIMENTALLY INDUCED LOCALIZED INFLAMMATORY REACTIONS IN THE LIVER*

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From the histophysiologic point of view, Maximow [1] arranged the connective tissue and the blood of vertebrates into three vast groups: (1) fixed, highly differentiated cells which produce the fibrous intercellular substance in connective tissue, known as fibrocytes; (2) fixed or free cells which possess marked ability for phagocytosis and are especially prominent in the liver, spleen, lymph nodes and bone-marrow, and (3) hemocytes, which include all circulating elements in the lymph and blood stream. As early as 1902, Maximow [2] recognized three principal cell types in any field of inflammation. These are: (1) fibroblasts, or the common connective tissue cells; (2) polymorphonuclear leukocytes, and (3) the mononuclear exudate cells, or polyblasts as he called them, perhaps the most important in any inflammatory reaction of defense. The origin of these three types of cells and their ontogenetic relationships is a problem concerning which the opinions of leading cytologists are still greatly at variance.

It is not our purpose to review the extensive literature covering the details of the experimental data that are available. The reader is referred to the articles of Maximow and Bloom [3] for full bibliographies and complete interpretation. Our interest in the problem was not immediately related to the relative potency of the connective tissue cell or to the origin of the various kinds of cells which appear in any generalized inflammation. But since the Kupffer cell of the liver is a mesenchymal cell, placed in group 2 of Maximow's classification, we were interested to know the extent to which these cells would react in the restoration of aseptically induced hepatic lesions. The reaction of the stellate cells in the liver to a bacterial invasion has been studied,

* Submitted for publication, Jan. 4, 1929.

* From the Division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Maximow, A. A.: Morphology of the Mesenchymal Reactions, Arch. Path. **4**:557 (Oct.) 1927.

2. Maximow, A. A.: Experimentelle Untersuchungen über die entzündliche Neubildung von Bindegewebe, Jena, Gustav Fischer, 1902, vol. 7, p. 262.

3. Bloom, William: The Origin and Nature of the Monocyte, Folia haemat. **37**: 1, 1928.

as well as the response induced by the introduction of foreign bodies into the hepatic parenchyma. Bloom [4] reported observations on the Kupffer cells in a study of abscesses induced by infection with *Bacterium monocytogenes,* whereas Biebl [5] reported his observations on the reaction of the reticulo-endothelial cells in the liver to foreign bodies in the form of autogenous transplants, such as kidney and muscle.

The Kupffer cells of the liver are a part of the system of fixed histiocytes which are localized in various parts of the body; they are identified and grouped, to a large extent, by their behavior toward vital dyes. Kupffer cells react to supravital staining with neutral red in the same way as wandering cells of common connective tissue, and, in tuberculous lesions of the liver, they have been shown to hypertrophy, proliferate mitotically and become free histiocytes in the blood stream. They may form epithelioid cells, and it is not uncommon to see in vital staining in rabbits the fusion of such free epithelial cells into giant cells. All cells lining the hepatic sinusoid are not actively phagocytic at any one time. Following one or two injections of a suspension of graphite or of any one of the vital dyes, a few Kupffer cells may always be seen literally packed with granules and projecting far into the lumen of a sinusoid, while others, apparently inactive, lie closely applied to the parenchymal cell. Following repeated injections, however, many of these hitherto resting phagocytes become active; but even in the face of prolonged vital staining, one invariably sees a few quiescent histiocytes lying along the parenchyma, without evidence of phagocytosis. It has been stated that these cells, following extensive phagocytosis, desquamate, enter the blood stream as blood histiocytes and are filtered off in the lung. However, we have identified Kupffer cells with particles of graphite in hepatic lobules of rabbits, six to eight months following intravenous injection. The origin of these stellate cells in the sinusoid is uncertain. They probably do not arise from common vascular endothelium, the presence of which, within the hepatic lobule, may rightly be questioned. Should they arise in situ, we would expect to encounter mitotic figures more frequently than we do. Elliott [6] suggested that these histiocytes of the reticulo-endothelial system, lining vascular sinusoids, may be blood monocytes which adhere to the walls and remain temporarily fixed. This conclusion is open to question, and yet there are many experimental data to lend it credence.

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4. Bloom, William: The Formation of Abscesses in an Infection with Bacterium Monocytogenes, Arch. Path. **6**:995 (Dec.) 1928.

5. Biebl, Max: Eine experimentelle Bindegewebstudie am Reticuloendothel der Leber, Deutsche Ztschr. f. Chir. **218**:306, 1929.

6. Elliot, Caliste: The Origin of the Phagocytic Cells in the Rabbit, Bull. Johns Hopkins Hosp. **39**:149, 1926.

De Haan and Hoekstra,[7] in a series of ingenious experiments, concluded that the Kupffer system in the liver is not stable, but that it is constantly changing in the number of its components. They directly identified the Kupffer cell with the clasmatocyte. After developing large numbers of mononuclear cells in the peritoneal cavity of rabbits by injecting large quantities of a solution of sodium chloride, they marked the cells so that subsequently they could be identified by injecting trypan blue. These large mononuclear cells, which contained granules of trypan blue, were then injected into the portal stream of another rabbit. Sections of the liver of the second rabbit contained typical Kupffer cells with the granules of trypan blue within them, although the spleen and the lung did not contain any of the injected cells. The authors concluded that the injected mononuclear cells had been intercepted by the liver and had transformed into functional Kupffer cells. They observed all transitions from the free spherical mononuclear cell, which they introduced, to the fixed oval or elongated cell, closely applied to the hepatic trabecula.

The relation of the Kupffer cells of the liver to the cells of the blood stream was recently rather unduly emphasized by Malyschew,[8] who ascribed to them a widely diversified potentiality. In aseptic lesions of the liver, according to this author, these cells may hypertrophy, reorganize and differentiate into promyelocytes, myelocytes, megakaryocytes, monocytes and fibroblasts; and they may even proliferate and regenerate vascular capillaries. In fact, from these observations, one might well conclude that the Kupffer cell could serve as a stem cell from which all other hemocytes could arise. Siegmund-Köln,[9] in studies following the injection of living colon bacilli into the portal vein, also concluded that the Kupffer cells, after desquamating, gave rise to polymorphonuclear leukocytes, conclusions which since have been proved false.

Bungeler and Wald,[10] in studies on inflammatory lesions, were unable to substantiate Malyschew's conclusions. These authors regarded the stellate cell as a highly differentiated cell which may give rise to monocytes, but never transforms into polymorphonuclear leukocytes.

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7. De Haan, J., and Hoekstra, R. A.: Ersuche über die Herkunft und die Deutung des Kupfferschen Systems der Leber, Arch. f. exper. Zellforsch. **5**:35, 1927.

8. Malyschew, B.: Ueber die Rolle der Kupffer'schen Zellen bei aseptischer Entzündung der Leber, Beitr. z. path. Anat. u. z. allg. Path. **78**:1, 1927.

9. Siegmund-Köln: Untersuchungen über Immunität und Entzündung, Verhandl. d. deutsch. path. Gesellsch. **19**:114, 1923.

10. Bungeler, W., and Wald: Beiträge zur Herkunft der polymorphkernigen Leukocyten. Die Bedeutung der Kupfferschen Sternzellen bei der Entzündung, Virchows Arch. f. path. Anat. **270**:150, 1928-1929.

Whereas Schilling[11] in reported observations of cases of monocytic leukemia described the transformation of Kupffer cells into monocytes, Bloom,[4] in studies on experimental abscesses in the liver, could not recognize any participation by these stellate cells in the marked production of mononuclear exudative phagocytes. Bloom regarded these exudative mononuclear cells of a hematogenous source as being of lymphocytic or monocytic origin. Biebl, in studies on the reaction of the reticulo-endothelial cells of the liver to autogenous transplants, attributed the mononuclear reaction that ensues to proliferation of the polyblasts of the periportal spaces and the Kupffer cells of the sinusoids.

MATERIAL AND METHODS OF STUDY

In order to determine the reaction of any given cell to a foreign stimulus, it is essential that it be marked in some way to identify it among other cells with perhaps equal potency. Accordingly, in this study the injection method was employed to delineate the phagocytic cells of the liver, prior to inducing the aseptic lesion. A suspension of graphite frequently employed in our laboratory for intra vitam studies was injected intravenously into an animal from two to three days before the operative procedure. Into some animals only small amounts, 2 or 3 cc. for each kilogram of body weight, were injected; into others, larger amounts, sometimes as high as 25 cc. for each kilogram of body weight, were injected. In this way, the reaction of a liver in which the phagocytic cells were only lightly speckled with graphite could be followed, as well as if the cytoplasmic bodies were completely distended. Within a short time following these injections, laparotomy was performed under ether anesthesia, and a hot instrument, 2 mm. in diameter, was introduced into the hepatic substance. From three to four such puncture wounds were made in the liver thus exposed. At intervals following the operative procedure, the animals were killed; the blocks of hepatic tissue containing the sites of injury were removed, fixed in Zenker-formaldehyde solution and stained with hematoxylin and eosin, van Gieson's stain, and Mallory's connective tissue stain. Studies were made at one hour, three hours, six hours, ten hours, twenty-four hours, forty-eight hours, seventy-two hours, one week, two weeks, three weeks and one month following the production of the aseptic lesion in the vitally stained liver. Rats, rabbits and dogs were used, and although the results attained were essentially identical in these animals, this report will be restricted to the reactions encountered in the liver of the albino rat.

EXPERIMENTAL OBSERVATIONS

Kupffer Cells in Normal Liver.—Following the injection of the preparation of graphite and prior to the operation, sections of the liver showed that the injected material had been taken up by the Kupffer cells which line the hepatic sinusoids and that most of these phagocytic cells contained graphite in varying amounts (fig. 1). Many of them, however, had been inactive and could be identified along the walls of sinusoids in their resting condition. The graphite-laden cells varied in size. Their elongated processes might frequently extend over two or three hepatic cells, and often small pseudopodial processes reached into intervals between adjacent hepatic cells. Occasionally, well laden cells fixed at places

11. Schilling, Viktor: Der Monozyte in trialistischer Auffassung und seine Bedeutung im Krankheitsbilde, Med. Klin. **1**:563, 1926.

to the sinusoidal wall projected into the lumen of the sinusoid, and in some instances the processes appeared to have been retracted; the cell was spherical, presenting every evidence of a mononuclear cell free in the blood stream. Occasionally, from forty-eight to seventy-two hours after injection, graphite-bearing cells appeared in the interlobular tissue surrounding the blood vessels and the bile ducts. These cells resembled, both in size and staining reaction, the mononuclear cells so often encountered free in the lumen of the sinusoid, and their presence within the periportal tissue might be due to a migration from the site

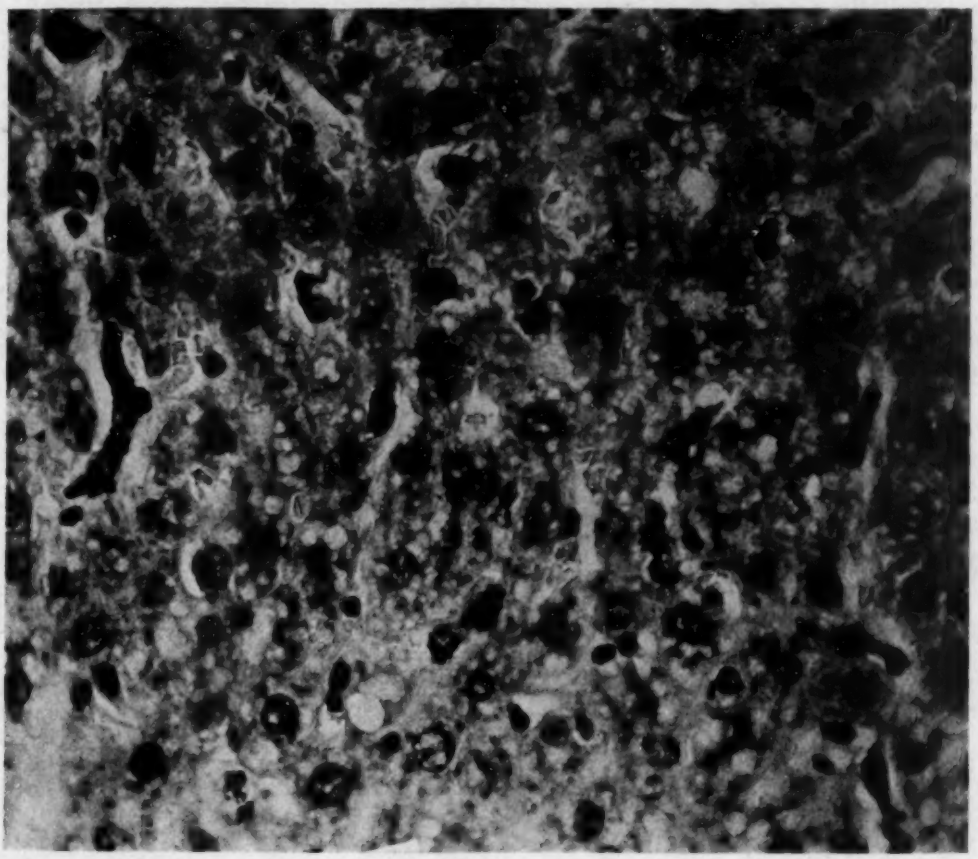

Fig. 1.—Normal rat's liver after an injection of graphite prior to injury (× 300).

of origin within the lobule, or the blood stream, to the mesenchymal cells surrounding the interlobular vessels. The relation of the stellate cells to these mesenchymal cells of the periportal spaces, which proliferated so abundantly following the production of the lesions, will be considered more in detail elsewhere in the paper.

Kupffer Cells in Injured Liver One Hour After Injury.—One hour after the injury to the hepatic substance with a hot needle, marked congestion extended throughout the injured region. A prominent zone of congested hepatic substance

separated the inflamed region from the normal hepatic tissue surrounding it. The hepatic cells throughout the site of the lesion were necrosed and spindle-shaped and contained oval, elongated nuclei. Kupffer cells within the region were destroyed, and scattered granules of graphite abounded throughout. Polymorphonuclear infiltration had not yet taken place.

Hepatic tissue peripheral to the lesion was not essentially unlike that prior to operation. The hepatic sinusoids were not as yet congested, but the phagocytic cells, for a considerable distance peripheral to the lesion, were no longer stellate.

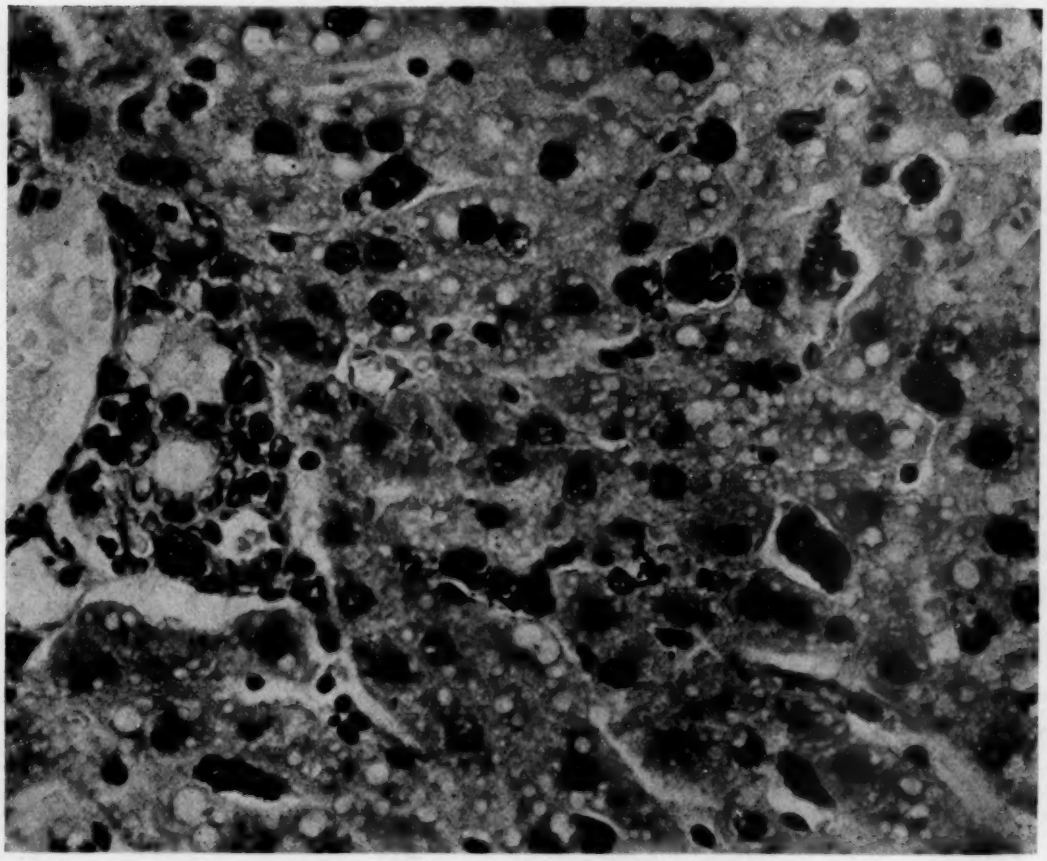

Fig. 2.—Hepatic parenchyma, adjacent to site of injury, one hour after operation (× 300).

Their processes had been retracted, the cells were more spherical, many lay free within the lumen, and there was some evidence that migration of these cells had begun (fig. 2). This pertains equally to those Kupffer cells of the sinusoid which did not contain graphite. They, likewise, were swollen, lay frequently free in the lumen, and showed evidences of migration, either toward the lesion, or, more commonly, toward the interlobular connective tissue spaces. Hyperactivity of these regions as centers or foci for cellular proliferation, so extensive in the later repair of the lesion, was not manifest as yet.

Six Hours.—Six hours after the injury, the cytoplasmic bodies of the necrotic cells were largely disintegrated, and the nuclei, for the most part, had disappeared. A few polymorphonuclear leukocytes extended throughout the lesion, and large numbers of mononuclear graphite-laden cells abounded throughout the perinecrotic tissue. Many of these lay free in the sinusoids; others appeared to lie between hepatic cells within trabeculae; many others lay among the mononuclear cells now proliferating from the mesenchymal cells in the perilobular spaces. This cellular proliferation in the portal spaces was characteristic; but mitotic figures were exceedingly rare, and one wonders whether amitotic cellular division may not be the rule. Binucleate cells often were encountered, and elongated shapes were such as often to suggest amitosis.

Twenty-Four Hours.—Twenty-four hours after injury, the organization of the lesion was well advanced. In the center of the necrotic region was a fibrinous, bloody exudate containing many polymorphonuclear leukocytes and a few monocytes. These cells had phagocytosed many of the granules of graphite which had been scattered throughout the site of the lesion at the time of injury. Throughout portions of the necrotic region toward the periphery, there were numerous foci, or centers, in which the neutrophilic granulocytes were exceedingly abundant; whereas, at the periphery of the necrosed region, adjoining the normal parenchyma, small nests of mononuclear cells had accumulated. Many of these mononuclear cells contained graphite; many did not. Marked congestion characterized the uninjured, adjacent hepatic parenchyma. The sinusoids were wide open, and the Kupffer cells which yet remained attached projected far into the lumen. The whole field differed essentially from that of a liver into which graphite had been injected, prior to the operation. Pigmented cells were not evenly distributed, but were more concentrated, especially in the interlobular spaces around the bile ducts and blood vessels, centers which acted as prominent foci for the proliferation of large numbers of mononuclear cells.

Forty-Eight Hours.—The center of the necrotic region, at forty-eight hours after injury to the liver, was largely cleared of free graphite and cellular fragments, owing essentially to the phagocytic activity of both the granulocytes and the agranulocytes. At this time, most of the granulocytes were massed into a wide circular band extending throughout a region midway to the periphery of the necrotic region, ingesting free graphite and fragmented hepatic cells. At the periphery, but within the necrotic region adjacent to the normal parenchyma, many mononuclear cells, both with and without graphite, largely ameboid, contributed toward the formation of a delineating wall (accentuated in later stages) which separated the necrotic from the normal tissue. Graphite-laden cells in the hepatic parenchyma were less frequent, and many appeared to be migrating through hepatic trabeculae, either toward periportal spaces or directly to the lesion.

Seventy-Two Hours.—The reaction at the site of injury in a rat's liver, seventy-two hours after operation, differed only slightly from that at forty-eight hours. The region of fibrinous exudate was larger and the circular zone of granulocytes was replaced by a group of active granulocytic centers (fig. 3). The deposition of mononuclear cells around the necrotic region, delineating it from hepatic parenchyma, was more extensive; so that a wall, from four to five cells thick, was formed. Granulocytes were absent from this peripheral zone of mononuclear cells. Most of the cells forming this zone contained graphite; a few did not, and it appeared to us that these cells had migrated to the site of injury from the surrounding hepatic parenchyma. Many of these mononuclear cells, relatively spherical in earlier stages, were largely spindle-shaped, and elong-

ated cytoplasmic processes with collagenous intracellular material extended out from ovoid, centrally placed nuclei for considerable distances, forming connective tissue cells with fibrous processes. Most of these elongated cells contained very small particles of graphite which might be identified out in the finer protoplasmic extensions, and many did not; thus it appeared to us that the extensive capsule of fibrous tissue, identified in later stages, had its inception at this stage, arising from mononuclear cells which had migrated from the hepatic sinusoid and from the local histiocytes of the perilobular spaces to the site of injury. If proper

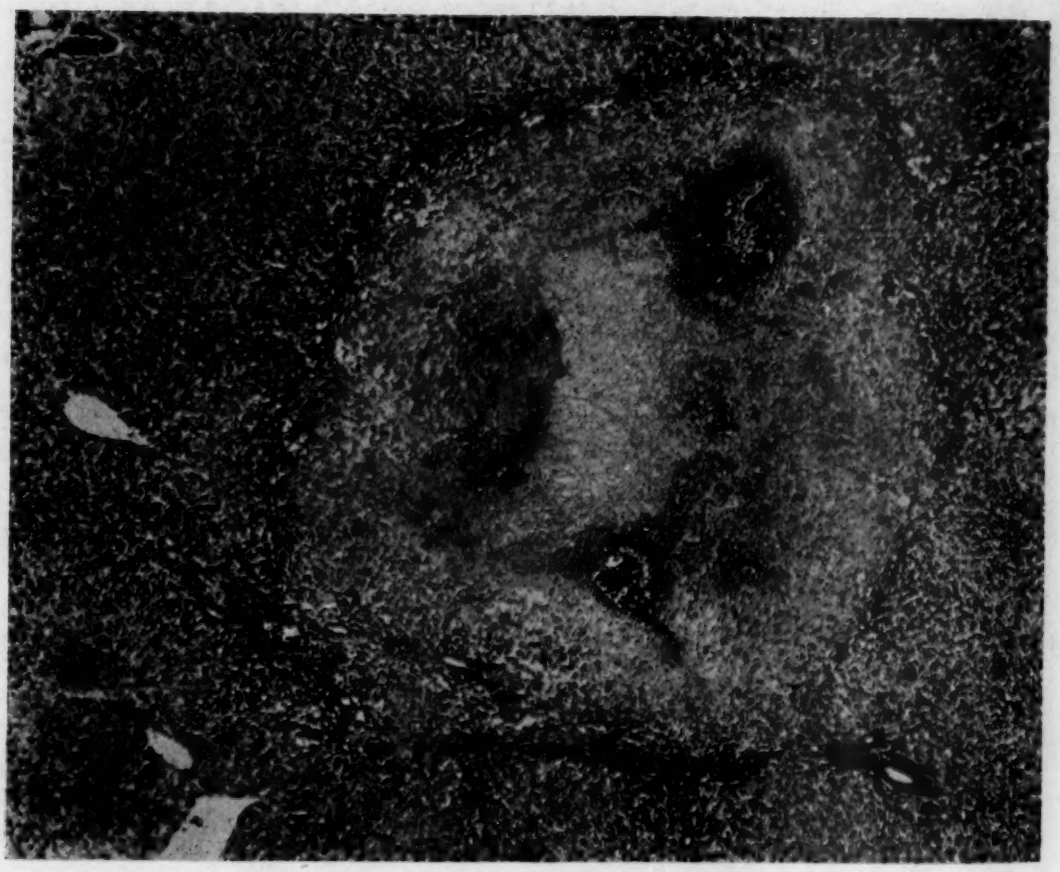

Fig. 3.—Organization of entire lesion and adjacent parenchyma at seventy-two hours after operation (× 48).

sections were secured, one often identified a "streaming" movement of these mononuclear cells from the periportal regions, along the perivascular spaces in the interlobular regions to the site of the lesion. Littoral cells of the sinusoid probably did not migrate for any distance in the lumen toward the inflamed area; but we were inclined to believe that there was a migration free from the sinusoid, directly through parenchymal tissue, to adjacent perivascular mesenchyme, and thence these cells, together with polyblasts which were proliferated from parent histiocytes around the blood vessels, migrated toward the site of inflammation.

Five Days.—A microscopic section of an inflammatory lesion and its surrounding hepatic parenchyma five days after operation revealed two essential contrasts with that of a like lesion of seventy-two days' duration. Most apparent, perhaps, was the reduction in graphite-laden cells throughout the hepatic substance peripheral to the lesion. Scattered, pigmented cells abounded in the five-day stage, but these were appreciably less in the hepatic parenchyma at this time and suggested a breaking away, or a migration, of those cells which had so extensively phagocytosed the injected particles of graphite. In further contrast with the

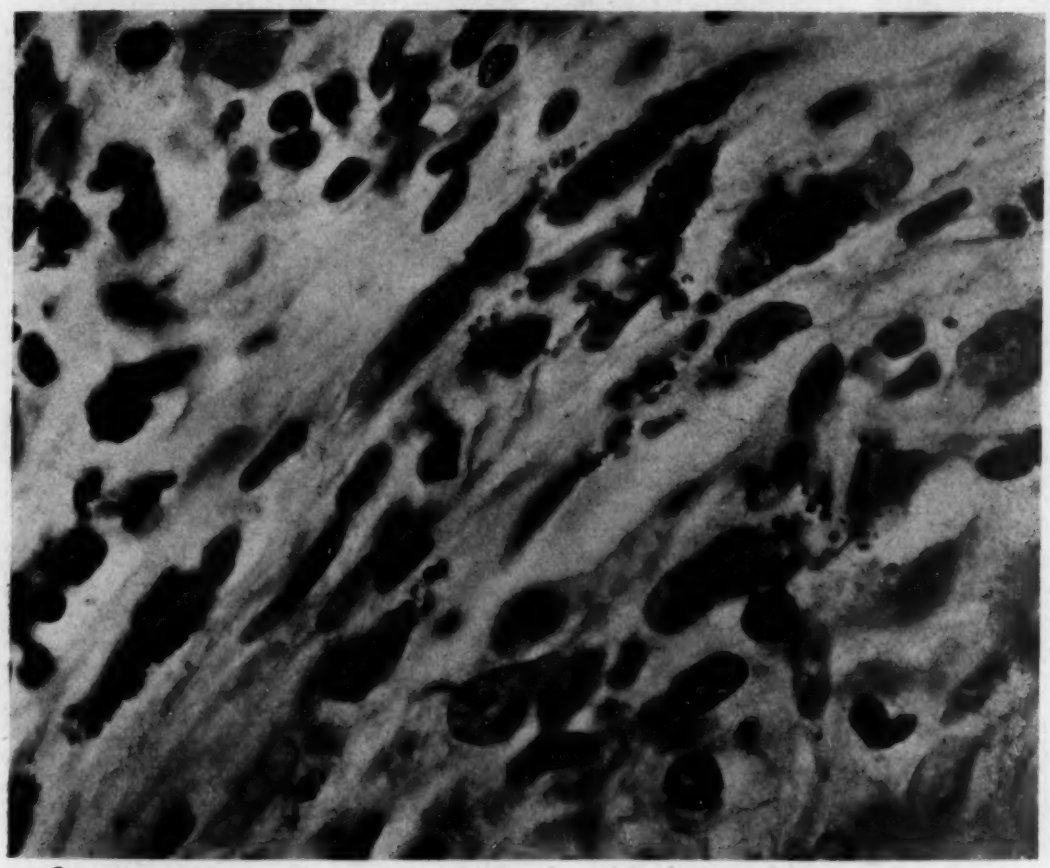

Fig. 4.—Portion of capsule, surrounding lesion, six days after operation; elongated, spindle-shaped, graphite-laden cells are seen (× 1400).

earlier, seventy-two hour stage, the wall of limiting capsule surrounding the lesion stood out in marked contrast with both the acidophilic, necrosed hepatic tissue and with the more darkly stained, normal parenchyma. The size of the wall had increased to a layer from ten to twelve cells thick, all cells of the mononuclear series; but more striking, perhaps, was the large accumulation of particles of graphite which were gathered into the cells which comprised this wall. Many of these mononuclear cells were fibroblast-like, spindle-shaped, with long, fibrous processes (fig. 4), whereas others were more spherical still, with

amoeboid characteristics. There were no centers of granulocytic activity, and such neutrophilic leukocytes as did abound were distributed somewhat generally throughout the necrotic area, but they never were encountered in the capsule of the lesion. Mononuclear cells, however, occurred within the necrosed parenchyma, probably moving in somewhat from the capsule, as well as arising in situ from mononuclear cells of the blood or from local histiocytes not destroyed at the time of injury.

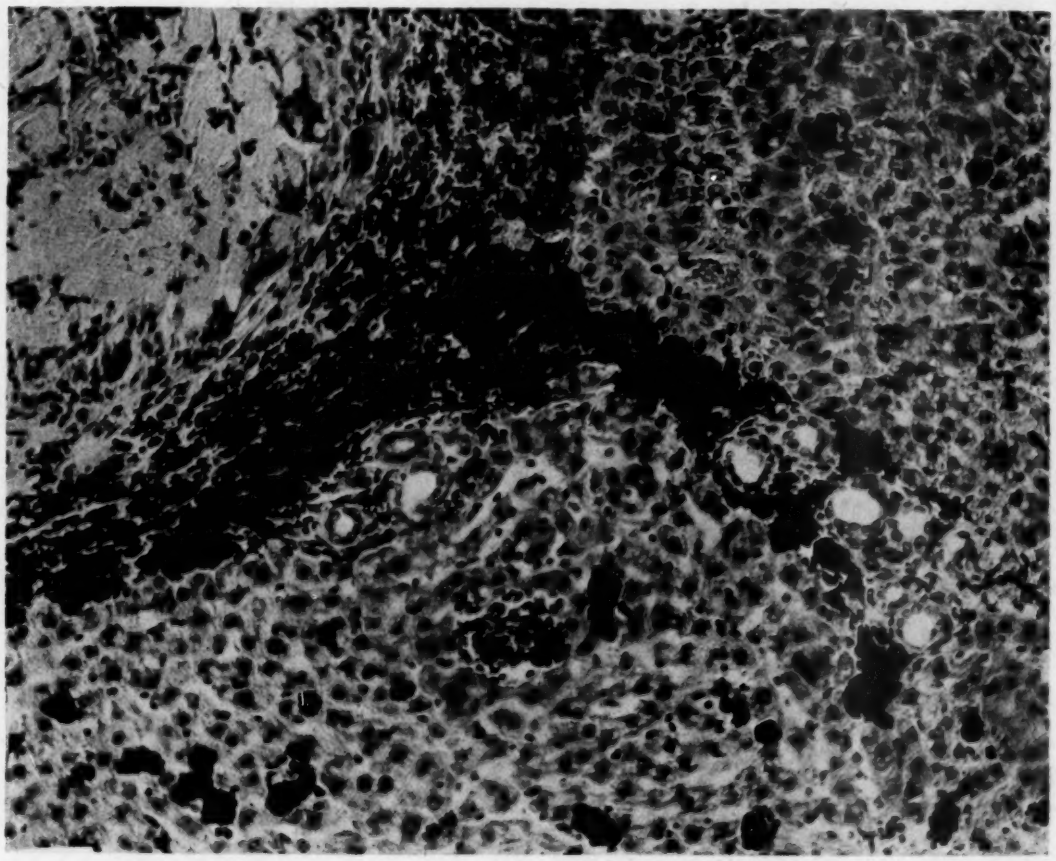

Fig. 5.—Portion of capsule surrounding lesion twenty-one days after operation in a rat which had received a heavy injection of graphite (× 200).

Mesenchymal Cell Proliferation in Liver.—Cellular proliferation from the local mesenchymal cells of the periportal spaces appeared to be of a rhythmic nature. Proliferation of these cells was marked during the earlier phases of the cellular response to the injury; and again, two weeks after injury, zones of mononuclear cells, many times normal proportions, surrounded the interlobular bile ducts and blood vessels. Mitosis in these zones was not common, and yet occasional mitotic figures were encountered. Whereas one might hesitate to ascribe these marked increases in numbers of cells to amitosis, yet the elongated shape of the nuclei so often encountered was most suggestive. Two types of

mononuclear cells characterized these proliferative zones. There were small, darkly stained basophilic cells with compact chromatin and larger cells, with lightly stained nuclei and a loosely arranged network of chromatin. Scattered throughout these zones were many graphite-laden cells, for the most part of the larger type, which seemed, to a large extent at least, to have migrated to these centers from the closely adjacent sinusoid. The majority of the cells in these zones, however, were without graphite, and, we felt, had arisen in situ from the local histiocytes which abounded in the normal liver and from lymphocytes which, no doubt, had migrated from the hepatic sinusoids and blood vessels to these centers, changing into monocytes and into tissue histiocytes. Typical blood monocytes were not abundant in these proliferative zones, and yet one might identify a sufficient number of intermediate forms to indicate that, in accordance with Bloom's [12] (1927) conclusion, monocytes arise by transformation of the smaller lymphocytes. Furthermore, it was impossible to determine whether these polyblasts were of hematogenous or histiocytic origin.

In rats that had received rather heavy injections and the livers of which had been studied at two and three weeks following injury, the migration of these graphite-laden mononuclear cells to the inflamed region had been so extensive that a complete, heavily infiltrated wall entirely delineated the site of injury from the surrounding hepatic parenchyma. This reaction was so pronounced that in some instances so effective a barrier had been produced as to form a black wall around the region of necrosis (fig. 5). Furthermore, the migration of graphite-laden cells from the peripheral parenchyma to this wall was frequently so extensive as to form, in histologic section, heavily infiltrated paths leading toward the necrotic region as a center (fig. 5). These paths, along which mononuclear cells passed to the lesion, frequently extended from the peripheral parenchyma widely remote from the lesion.

COMMENT

Supravital technic or other refined methods designed to differentiate cells types have not been employed in this study; and accordingly definite proofs of cellular lineage have not been presented. We wished rather to know whether the phagocytic cells of the liver, recognized mesenchymal cells, could well function in the organization of aseptically induced hepatic inflammatory lesions.

The injection method, as a means for the identification of cells, is a fairly satisfactory one. To be sure, reticulo-endothelial elements throughout the body phagocytose injected materials as effectively as do those within the liver, so that phagocytic cells in the spleen or bone-marrow, for example, are labeled in a manner similar to those in the liver. It is not likely, however, that these fixed histiocytes, which may or may not become free cells from time to time, will essentially modify a slight inflammatory reaction within the liver. Circulating lymphocytes and monocytes have been shown to be sharply differentiated from these histiocytes; and although under conditions of pathologic stress monocytes

12. Bloom, William: Transformation of Lymphocytes of Thoracic Duct into Polyblasts (Macrophages) in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **24**:567, 1926-1927.

may transform into histiocytes and fibroblasts, their origin is essentially divergent. Accordingly, we felt that by marking the stellate cells of the liver by their ability to engulf foreign bodies, we could well follow their activity and feel reasonably sure that we were dealing with the cell that was the original phagocyte in the liver and not cells of the lymphoid group.

Accordingly, with this consideration of the method, intravenous injections of a preparation of graphite were made in a large series of rats, so that at least a majority of the Kupffer cells contained varying amounts of the black pigment. Slight puncture wounds were then made in the hepatic substance, under aseptic conditions, and the cellular reactions were studied for a period of one month thereafter.

Cappell [13] stated that removal from the blood stream of various materials by the liver is due chiefly to the endothelium and stellate cells of the sinusoids. It is questionable whether hepatic sinusoids are lined with regular endothelium. Occasional, flattened, endothelial-like cells lie along the hepatic parenchyma, and we have in the past, no doubt, identified these cells as parts of an hepatic endothelium. Even with special staining methods, however, such as the Rio Hortega or the Bielschowsky, we have not been able to identify a continuous cytoplasmic structure along the margin of the sinusoid, and we feel that the hepatic parenchyma is separated from the blood stream by an incomplete partition consisting of a reticulum by means of which the Kupffer cells of the liver are held to the parenchyma of the liver.

Following injection of a suspension of graphite, about 3 cc., in a rat weighing 175 Gm., the blood stream was cleared within a few minutes, and the particles were found adherent to the cells lining the hepatic sinusoids. Within a few hours phagocytosis had taken place; the fine granules of graphite had been taken up and had now accumulated into the "segregation apparatus" within the cytoplasm of these cells. Particles of graphite were never identified in the local histiocytes of the periportal spaces immediately following an injection, and we do not believe that free graphite, under the conditions of our experiment, ever migrated through hepatic parenchyma to the periportal spaces.

In studies on the endothelium in the production of polyblasts in inflammation, Lang [14] concluded that carbon particles may enter endothelial cells, not as a result of phagocytosis, but more as a result of physical properties associated with surface tension. He concluded that particles of carbon merely pass through endothelium and are then taken

13. Cappell, D. F.: Intravitam and Supravital Staining, J. Path. & Bacteriol. **32**:595, 1929.

14. Lang, F. J.: Rôle of Endothelium in the Production of Polyblasts (Mononuclear Wandering Cells) in Inflammation, Arch. Path. **1**:41 (Jan.) 1926.

up by cells surrounding the capillary wall. It is possible that the presence of graphite-laden cells in the periportal spaces of our experimental rats is explained in that way; namely, that particles had forced their way through the endothelium of the interlobular capillaries and had been engulfed by the polyblasts surrounding them. We have never seen particles of graphite in these endothelial cells, however, and the fact that the number of graphite-laden cells in the periportal spaces was so much greater in the later stages, long after the blood stream had been freed of floating particles, leads us to conclude that the majority of these graphite-laden cells had migrated from the blood stream and the sinusoids.

The inflammatory lesions were induced in the livers of these rats soon after injection; thus, in most cases, they were induced prior to the migration of the phagocytic cells into the periportal spaces. Within a few hours, however, following the injury to the parenchyma of the liver, the Kupffer cells in the sinusoids around the site of the lesion became swollen, projected far into the lumen and retracted their cytoplasmic processes. At this time, large mononuclear cells lay free in the blood stream; and, since these cells presented a staining reaction and a distribution of graphite identical with that of the attached phagocytic cells, one may conclude that these cells in the lumen were desquamated Kupffer cells. This observation, of course, has been made frequently by other workers.

During this initial response by the Kupffer cells of the normal parenchyma, slight changes took place within the inflamed region. The necrosed hepatic cells were greatly swollen; they rapidly disintegrated, and particles of graphite, contained within phagocytic cells prior to operation, were scattered throughout the lesion. Granulocytes did not appear for six or eight hours, but in the twenty-four hour lesion they were abundantly scattered throughout the more central portion of the necrosed parenchyma, engulfing exudate and graphite residue. Mononuclear cells were few within the center of the lesion, although at the periphery, along the line of transition from necrotic to normal parenchyma, many such cells abounded. These mononuclear cells, we felt, were local histiocytes which were within the zone of hepatic parenchyma immediately surrounding the lesion.

Within twenty-four hours after the operation, proliferation of the local histiocytes or polyblasts within the periportal spaces had taken place, so that a large number of small mononuclear cells surrounded the blood vessels and the bile ducts. Interspersed among these were numbers of cells which contained the graphite much as did the free cells in the sinusoids and the stellate cells still attached. These graphite-laden cells of the portal spaces, we believe, had migrated either directly

through hepatic parenchyma or from the blood stream to these regions. The finding of occasional mononuclear cells, containing graphite within the hepatic trabeculae, forces the opinion that an actual migration between adjacent hepatic cells of a trabecula may take place. Although many graphite-laden cells abounded in the portal spaces, many such cells still remained in the adjacent sinusoids and many phagocytes were as yet fixed to their original position; so that all Kupffer cells did not immediately desquamate. All mononuclear cells within the sinusoids, fixed or free, did not contain graphite. In fact, many did not, but we were unable to determine whether these Kupffer cells, apparently new in the field, had arisen as a proliferation of previously existing cells, or whether, as de Haan and Hoekstra thought, they had migrated to this position.

The further cellular reaction to the inflammatory lesion consisted in but an elaboration of the processes already initiated. The infiltration of polymorphonuclear neutrophils became exceedingly marked, especially within the central portions of the lesion where phagocytosis of cell fragments and particles of graphite rapidly occurred. Granulocytes were rare in the peripheral fourth of the circular lesion, a zone in which the mononuclear exudate cell was most active. Lesions at forty-eight hours and seventy-two hours after operation showed a heavy infiltration of such cells, sufficient to form a wall from 6 to 10 cells thick. Many of these cells contained graphite, many did not, and we believe that they had appeared there, coming partly from preexisting mononuclear cells, but largely from cells which had proliferated from the local histiocytes of portal spaces and wandering phagocytes from hepatic sinusoids. Our evidence for this lies essentially in the frequent identification of the "streaming phenomenon" in which cells, both with and without graphite, appeared to be migrating in mass formation toward the lesion. We do not presuppose that the presence of graphite within these mononuclear cells at the inflammatory site indicates, in every case, direct lineage to the phagocytic cell of the sinusoid; for the residual graphite free within the lesion at the time of operation was no doubt ingested by the mononuclear cells in situ. However, we do feel that many of the graphite-laden mononuclear cells traversing the trabeculae, or migrating together with the proliferating local histiocytes toward the lesion, there to contribute toward its encapsulation, were, to a large extent, directly related to the Kupffer cells of the sinusoid. In his studies on the cellular reaction toward the transplantation of foreign tissues into the hepatic parenchyma, Biebl observed this same sort of reaction that we have encountered in inflammatory lesions; namely, marked proliferation of the local connective tissue cells and migration, together with many Kupffer elements, toward the site of the transplant.

This inflammatory reaction within the liver was not unlike that which arises in lesions elsewhere in the body. The granulocytic reaction, occurring within from twenty-four to forty-eight hours following injury, appeared to be entirely independent of the mononuclear infiltration. There was no evidence to support the contention of Malyschew that the polymorphonuclear leukocyte arose from the Kupffer cell or other monocyte. The polymorphonuclear reaction was essentially restricted to the more central portion of the lesion and was apparently related in origin to comparable cells of the blood stream. These cells appeared within the lesion, engulfed foreign materials, and then disappeared without evidence of further transformation. The site of the mononuclear response, on the other hand, was largely restricted to the peripheral portions of the lesion and appeared to take place largely as a migration from the normal hepatic parenchyma. Maximow [2] always claimed a dual origin for mononuclear exudate cells, and our observations appear to confirm this recognized concept. A certain number of these mononuclear exudate cells, we believe, arose from the lymphocytes and monocytes of the blood stream, which entered the inflammatory site, together with the neutrophils, and were found scattered throughout the lesion. The greater number, however, arose as a proliferation of the local histiocytes of the connective tissue and the Kupffer cells of the hepatic sinusoids which migrated to the lesion, there to take a position around the periphery, largely forming the delimiting capsule.

Throughout the proliferative centers around the bile ducts and blood vessels, various forms of cells without carbon could be identified. These ranged in size from small lymphocytes to the larger, typical monocyte with its reniform nucleus. These cells never contained the graphite, and we felt that all the stages in the development of the monocyte from the lymphocyte, an interpretation sustained by Bloom,[12] might be identified in these rapidly proliferating centers. To be sure, the migration of these granulocytes from the blood stream might not be excluded. It is reasonably certain, however, that the macrophages which we encountered in the hepatic parenchyma and in the periportal spaces did not form monocytes, but continued as wandering histiocytes or polyblasts until they transformed into fibroblast-like cells. The nonstoring mononuclear cells which we so often encountered, fixed or free in the sinusoids, probably did not give rise to monocytes, but continued as free wandering cells into periportal spaces as polyblasts. Bloom [3] favored the interpretation, however, that these nonphagocytic endothelial cells of the liver might produce hemocytoblasts and all myeloid elements.

Bloom [12] recently reported the transformation of lymphocytes of the thoracic duct into polyblasts and fibroblasts in tissue culture. An identical transformation, we feel, took place in the organization of these

aseptic lesions that we induced. On the third or fourth day after operation, when the mononuclear infiltration had formed rather a firm capsule around the necrotic tissue, the formation of fibroblasts was first evident. Within the wall surrounding the lesion, many mononuclear cells elongated, sent out cytoplasmic processes which frequently bifurcated, and formed typical fibroblasts. Many of these still contained the particles of graphite, which might be identified out in the distant cytoplasmic processes. Since fibroblasts were not ordinarily phagocytic, we must conclude that these spindle-shaped, graphite-containing cells were derivatives of the phagocytic cells of the hepatic sinusoid. Those fibroblasts which arose within the connective tissue capsule, devoid of graphite, were derivatives of the mononuclear cells, the lymphocyte, monocyte or polyblast, which had migrated into the inflammatory lesion from the periportal spaces.

SUMMARY

On the basis of a study of a series of inflammatory lesions in the livers of rats previously given moderate injections of a suspension of graphite to delineate the Kupffer cells, we believe that the Kupffer cell is not an ordinary endothelial cell, but rather a connective tissue cell of the histiocytic series. We question whether typical capillary endothelium exists in hepatic sinusoids.

Following phagocytosis of particles of graphite, the ingested material is agglomerated into larger granules distributed within the cytoplasm of the phagocytic cell. Within an hour following the production of an aseptic lesion in the liver, the Kupffer cells retract their processes, become swollen and spherical, and often detach themselves, as free mononuclear cells, and pass into the blood stream.

These macrophages now become free wandering histiocytes and may migrate, in some instances, to the site of the lesion, but more often to the adjoining regions around the portal spaces. At the same time, or shortly thereafter, the local histiocytes in the interlobular spaces rapidly proliferate and form many free, wandering cells or polyblasts. Typical monocytes also accumulate in these perivascular spaces and may arise as a transformation of migrated lymphocytes.

Polymorphonuclear leukocytes appear within the necrotic lesion and are exceedingly abundant after twenty-four hours. They are essentially restricted to the inner regions of the lesion, and do not change into other cells.

Mononuclear infiltration into the lesion is sufficient to form a capsule in from forty-eight to seventy-two hours after the production of the lesion. Further infiltration and transformation of these cells produce, at three weeks, a prominent, heavily carbonized wall separating the normal parenchyma from the normal tissue.

The mononuclear cells arise from two sources, from the agranulocytes of the blood stream and from the local histiocytes of the periportal tissue, including detached Kupffer cells.

Fibroblasts arise from mononuclear cells which form the wall of the lesion. These fibroblasts which contain graphite are transformed macrophages, developed largely from Kupffer cells. Those fibroblasts without graphite develop from the histiocytes of the periportal spaces and the transformed lymphocytes and monocytes of the blood stream.

LEUKOPLAKIA OF THE STOMACH

REPORT OF A CASE *

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The presence of squamous epithelium in gastric mucosa aside from its occurrence in connection with carcinoma or in the region of the cardio-esophageal junction has been, according to Borrman,[1] repeatedly described. The descriptions alluded to deal apparently with the presence of microscopic areas of squamous epithelium more or less accidentally encountered. Thus Hermann,[2] to whom Borrman refers, described such an area, 3 mm. long, in a microscopic preparation from a resected stomach, which was not detected grossly. Other authors similarly have described merely microscopic areas when they have spoken of the presence of squamous epithelium in the stomach. Herxheimer [3] in his discourse on the origin of heterologous cancroid of the stomach mentioned, in addition to metaplastic cells, misplaced squamous epithelial rests and groups of primitive undifferentiated cells which had persisted. Herxheimer made no reference to macroscopic groups of cells, and it can be safely inferred that he was discussing merely microscopic zones.

The presence in the stomach of islands of squamous epithelium of sufficient extent to form grossly visible plaques is apparently exceedingly rare and little known. Kaufmann [4] in his comprehensive special pathology made no reference to leukoplakia of the stomach; nor is this condition mentioned in the voluminous system edited by Henke and Lubarsch,[5] although Konjetzny [6] in his treatise of gastritis devoted several pages to the discussion of metaplasia of the gastric

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* From the Department of Medicine, University of Illinois College of Medicine.

1. Borrman, R.: Geschwülste des Magens und Duodenums, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, pt. 1, pp. 881-882.

2. Hermann, A.: Zur Frage der Epithelmetaplasie, Wien. klin. Wchnschr. **24**:168, 1911.

3. Herxheimer, G.: Ueber heterologische Cancroide, Beitr. z. path. Anat. u. z. allg. Path. **41**:348, 1907.

4. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, ed. 7 and 8, Berlin, 1922.

5. Henke and Lubarsch (footnote 1, editions 1926-1928).

6. Konjetzny, G.: Die Entzündung des Magens, in Henke and Lubarsch (footnote 1, pp. 768-1116).

epithelium. A thorough search of the literature led to the discovery of only one report of a case of leukoplakia of the stomach, and even here, although lengthy, the title does not include any statement which refers to the leukoplakia per se.

The aforementioned case, which was reported in 1899 by van Leersum and Rotgans,[7] concerns a young woman 22 years of age who dated her condition to seven years prior when she was required to remain in bed three weeks on account of gastric symptoms. She found it necessary in the course of time to eliminate rough foods and to restrict her diet more and more until finally she could tolerate only liquids. If she attempted to eat semisolid or solid foods, pain and vomiting ensued. It was stated that there was nothing in the physical examination or the history to point to syphilis except possibly the small stature of the patient whose measurements were those of a 13 year old girl. In the Ewald meal yeast cells, large bacilli and other bacteria were found. There was no free and 16 degrees total acidity. In the stomach washings, squamous epithelial cells were present in such large numbers and groups as to cover at times the entire microscopic field. Retained food was also recovered by lavage. The introduction of 200 cc. of fluid elicited pain and vomiting. Two operations were performed, the first a pyloroplasty, the second a total extirpation of the stomach with an anastomosis of the cardia to the duodenum. The distal two thirds of the stomach was transformed into a narrow tube, and the proximal one-third also was constricted but to a lesser degree. As nearly as can be determined from the description, the leukoplakia was noted in all parts of the stomach, although the exact extent is not stated. In two illustrations accompanying the article, stratified epithelium is seen to form the lining of the stomach wall.

In a recent article on gastric syphilis, I[8] submitted a detailed account of a case in which the resected portion of the stomach presented among other features a prominent white patch of squamous epithelium. This plaque was merely touched on in the description and only incidentally mentioned. On account of the rarity of this observation, a separate report seems warranted in order that the case may be indexed under the title of leukoplakia of the stomach and an adequate description of the condition be placed on record.

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7. Van Leersum, E. C., and Rotgans, J.: Extripatie der geheele maaglooze Oesophago-Duodenostomie. Endogastritis obliterans. De maaglooze Mensch, Nederl. Tijdschr. v. Geneesk. **35**:993, 1899.

8. Singer, H. A.: Syphilis of the Stomach with Special Reference to Its Relationship to Linitis Plastica, Am. J. Syph. **13**:391, 1929.

REPORT OF CASE

History.—R. M., a white man, 51 years of age, entered the Research and Educational Hospitals, March 22, 1928, with complaints of abdominal pain and vomiting of three years' duration. The progress of the disease was rather slow, particularly in regard to the vomiting, until shortly before entrance, when the patient was unable to retain even liquids. No history of a primary syphilitic lesion was obtained. Physical examination, except for a moderate degree of emaciation and a sense of resistance in the epigastrium, was negative.

Laboratory Data.—The fasting stomach contained 120 cc. of clear fluid which gave a negative test for free acid and a positive test for chemical blood. Following an Ewald meal, 450 cc. of poorly digested gastric contents was obtained, which was likewise devoid of free acidity. Occult blood was present in the stomach contents and also in the two stools examined. The x-ray picture showed an hour-glass constriction and canalization of the middle portion of the stomach. There was marked gastric stasis. The roentgenologist diagnosed probable carcinoma and suggested the possibility of syphilis. There was a moderate secondary anemia. The Wassermann and Kahn tests were reported positive (four plus).

Clinical Course.—After a few days of treatment with mercury and iodides, it soon became clear that the obstruction would eventually demand surgical intervention. Operation was therefore decided on. At the laparotomy, a thickened, shrunken stomach was found with the maximum involvement in the distal two-thirds, where many fibrous adhesions were encountered. An extensive resection was performed, leaving only the proximal 5 cm. of the stomach. The patient made an uneventful recovery and was discharged, April 21, 1928, in good condition. He appeared a year later in the clinic complaining of an independent condition and stated that since leaving the hospital he had experienced no gastric symptoms.

Gross Pathologic Observations.—The resected stomach was submitted to Dr. R. H. Jaffe, whose anatomic diagnosis was probable syphilis of the stomach. The gross characteristics can be described in brief as follows: The specimen had the appearance of a sausage with an enormously thickened, rigid wall. There was a deep constriction 2.5 cm. from the distal end, which produced an hour-glass deformity of the pyloric portion. The lumen of the stomach was greatly constricted, admitting in its widest part no more than two fingers. In its narrowest portion, which was located in the pyloric region, the diameter of the lumen was reduced to 0.4 cm. The maximum thickness of the wall of the stomach was 1.5 cm.; the minimum, 0.9 cm. The thickening was due mainly to an increase in the submucosa, which in places measured as much as 1 cm. On cross-section, the submucosa was glistening white and fasciculated. Fibrous extensions from the submucosa passed into and divided the underlying muscularis propria, giving the latter a lattice-work appearance. The serous covering and the mucous lining were slightly thickened, as seen in cross-section. The serosa on the anterior surface was roughened by adherent fibrous tags, whereas the posterior surface was smooth and glistening.

The appearance of the interior of the stomach was unique (fig. 1). In the proximal end of the specimen on the anterior wall was a raised, roughly quadrangular plaque (*A*), which measured 2 cm. and which by virtue of its snow-white color stood out prominently. The surface of this white plaque was finely wrinkled and puckered. Here and there, a radiating series of delicate folds emanated from a central depression. A small hemispherical yellowish nodule projected above the level of the plaque (this nodule which was included

in the portion removed for section consisted of fibrous tissue). The demarcation of the white plaque from the surrounding tissue was distinct. A diverticulum-like outpouching (*B*) appeared distal to the described patch and was separated from it by a linear zone of superficial ulcerations overlaid by fibrin. The remainder of the mucosa was for the most part mammillated and from gray-pink to pinkish red.

Microscopic Description of the Leukoplakia.—When the zone of squamous epithelium was approached (fig. 2), the mucosa exhibited a moderate diminution in the number of glandular elements. In the tunica propria adjoining the patch of leukoplakia were numerous eosinophils, round cells and plasma cells, scattered among which were enormous numbers of Russell bodies. The transition between the cylindric and squamous types of epithelium was an abrupt one. The squamous layer assumed its maximum thickness of from 15 to 20 cells practically immediately, but did not maintain this thickness throughout its extent.

Fig. 1.—The distal portion of the resected stomach opened along the middle of the posterior wall. A patch of leukoplakia (*A*) is separated from a localized outpouching (*B*) of the gastric wall by a linear zone of superficial ulcerations. The dotted lines indicate the extent of the plaque before a piece was excised for microscopic examination.

The lowermost layers of prickle cells presented a normal appearance, but those more superficially situated were swollen, poorly stained and devoid of intercellular protoplasmic bridges, but still retained their nuclei. The edematous epithelial cells were found in varying numbers in different portions of the plaque. The thickness of the squamous epithelial layer was directly proportionate to the size and number of the parakeratotic cells. The rête pegs were on the whole poorly developed and frequently entirely absent. Here and there, the squamous epithelium had undergone destruction. In one area, the defect was occupied by a plug of fibrin in the meshes of which were enclosed many leukocytes and a great deal of nuclear débris. Bordering such an ulcer was young granulation tissue

infiltrated by many round cells and plasma cells, eosinophilic and neutrophilic leukocytes and a few macrophages.

The basal layer of the stratum germinativum rested in most places on a somewhat edematous fibrous tissue which divided and separated the muscle bundles of the greatly hypertrophied muscularis mucosae. There was little infiltration of inflammatory cells in the subepithelial connective tissue, except at the margin of the transition from the columnar type and about the areas of ulceration. In some places intervening between the squamous epithelium and the muscularis mucosae was a wide tunica propria containing glandular elements between which

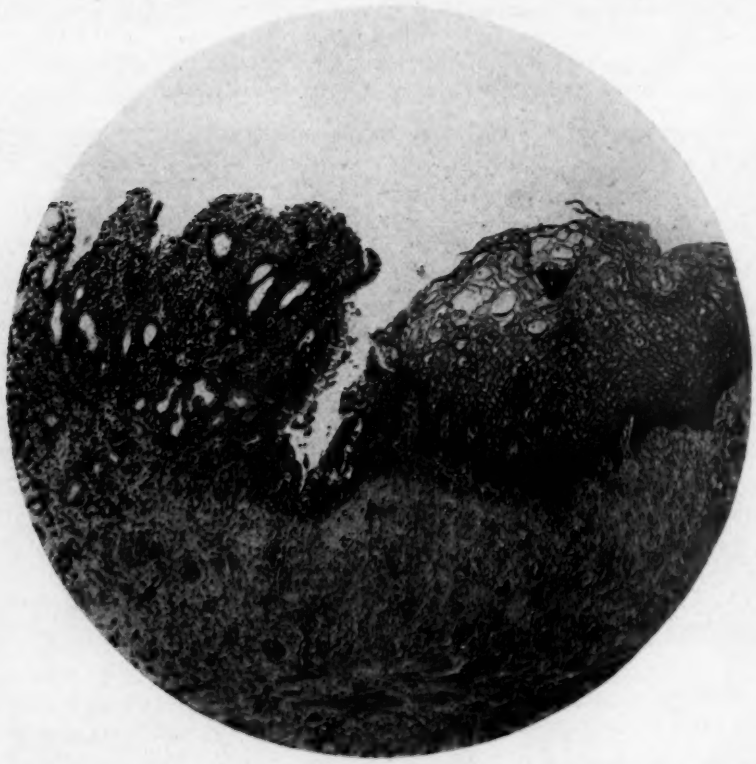

Fig. 2.—A section from the margin of the plaque illustrating the abrupt transition from cylindric to squamous epithelium.

were numerous inflammatory cells and Russell bodies. Occasionally, a gastric pit was seen communicating with the lumen of the stomach (fig. 3).

Microscopic Features of the Remainder of the Stomach.—The mucosa showed moderate atrophy of the glandular elements, diffuse cellular infiltration and multiple superficial ulcerations bordered by dense cellular infiltrates and young granulation tissue rich in capillary blood vessels.

The muscularis mucosae showed enormous increase in both the fibrous and the muscular elements and extensions of connective tissue into the overlying mucosa.

The microscopic features of the submucosa were prodigious thickening due to fibrous tissue overgrowth, thickening of the larger blood vessels due mainly

to muscle fiber proliferation in the region of the adventitia, focal panvasculitis affecting the veins to a far greater degree than the arteries, perivascular round cell infiltration of varying extent, and focal and diffuse round and plasma cell infiltrations.

In the muscularis propria were observed extensions of connective tissue from the submucosa invading and partially replacing the circular layer and mild infiltration along the fibrous septums.

Microscopically, the serosa showed slight connective tissue thickening with minor degree of cellular infiltration.

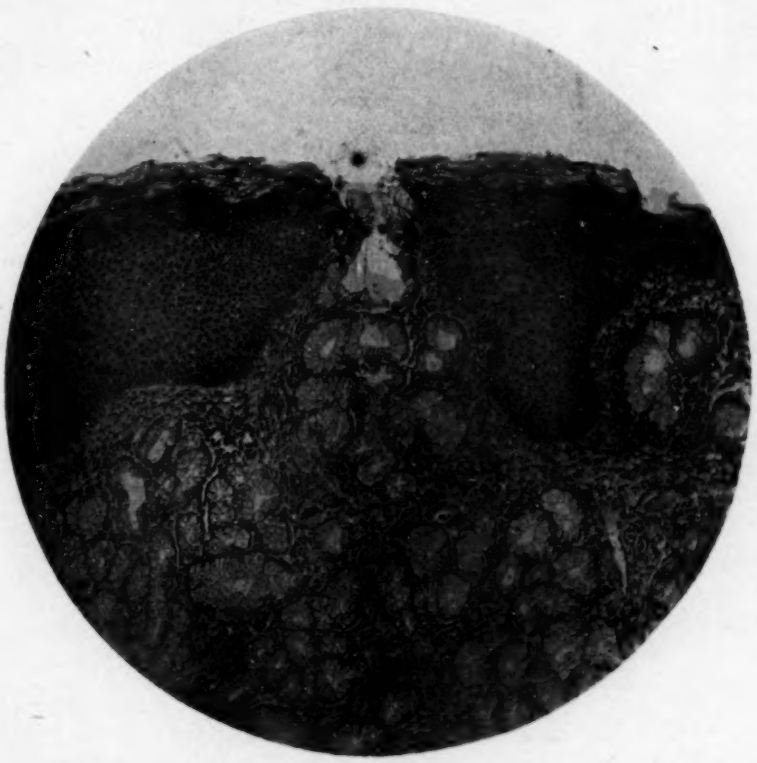

Fig. 3.—Squamous epithelium overlies tubules of the gastric glands and borders the mouth of a pit.

Bacteriology.—Levaditi and Ziehl-Neelsen stains were negative, respectively, for spirochetes and tubercle bacilli.

COMMENT

The problems in connection with leukoplakia of the stomach differ in no essential from the questions concerning leukoplakia elsewhere. The origin of the squamous epithelium in the case here reported in view of the presence of a gastritis is presumably metaplastic, the result of

prolonged irritation (see Fütterer [9]). It is also conceivable that the plaque originated from a group of primitive cells which possessed potentialities for differentiating into both the cylindric and the squamous types of epithelium which were simultaneously present. The rôle of syphilis is conjectural. The presence of syphilis was established in the case here reported. In the patient of van Leersum and Rotgans,[7] the only symptom or sign suggestive of syphilis was the lack of physical development. However, the contracted state of the stomach which led to the operation might well have represented the healed stage of a syphilitic gastritis. The relationship of leukoplakia to squamous cell carcinoma of the stomach involves the same considerations as leukoplakia elsewhere in the body.

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VARIATIONS IN THE NUMBER OF THE WHITE BLOOD CELLS ASSOCIATED WITH EXPERIMENTAL OBSTRUCTIVE JAUNDICE*

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A relationship between certain disorders of the liver and the monocytes in the circulating blood has been emphasized by Huffman, Lawrence and Jones.[1] These investigators found that the injection of pieces of sterile macerated rabbit liver suspended in a physiologic solution of sodium chloride into the peritoneal cavities of rabbits produced increases in the number of monocytes in the circulating blood. Further, they found that subcutaneous injections of phosphorus, a chemical known to be toxic to the liver, produced more marked increases in the number of monocytes in the circulating blood. Prior to this, it had been shown by Jones and Minot [2] and by Thewlis and Middleton [3] that there was an increase in the number of the circulating mononuclear cells in catarrhal jaundice in man. Holt [4] had demonstrated a similar reaction

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1. Huffman, M. M.; Lawrence, J. S., and Jones, Edgar: The Effect on the White Blood Cells of Intraperitoneal Injection of Whole Liver, Arch. Path. **7**:804 (May) 1929.

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in experimental obstructive jaundice in the rabbit. Accordingly, it seemed advisable to investigate this problem with particular reference to the relationship between jaundice and monocytosis. Holt did not produce complete obstruction to the flow of bile, since he ligated only one of the hepatic ducts. This procedure was followed by an increase in the number of monocytes in the circulating blood. We have produced experimental obstructive jaundice, both complete and partial, in a series of dogs and guinea-pigs. In general, complete obstruction was associated with only slight increases in the number of monocytes in the circulating blood, whereas partial obstruction was associated with more definite increases in the number of these cells.

EXPERIMENTAL METHOD

The observations were made on fifteen dogs and nine guinea-pigs. In all of these animals there was produced partial or complete mechanical obstruction to the passage of bile from the liver to the duodenum.

In ten of the fifteen dags, the common duct was ligated at two places and resected between the points of ligation. In three of the dogs, the common duct was ligated at one place only. In the remaining two dogs, one of the hepatic ducts was ligated.

Postmortem examinations of all the animals were made at the end of the period of investigation. Particular attention was paid to the following points:

1. Evidence of complete obstruction to the flow of bile. This was determined by the position of the ligature, the passage of a probe along the common duct to the point of ligature and, finally, by pressure on the distended gallbladder or the common duct and observation on the distal side of the ligature to determine whether any bile passed the point of obstruction.

2. Signs of infection of the peritoneal cavity. Infection was always looked for macroscopically, and cultures were taken whenever the animal had not been dead too long to render cultures unreliable. Unfortunately, five of the animals (dogs no. 1, 4, 5, 7 and 8) died several hours before autopsy, and no culture was obtained from the peritoneal cavity of any of these.

3. The presence of bile in the peritoneal cavity.

On the basis of these three conditions, the fifteen dogs were divided into four groups.

Group 1 includes dogs no. 4, 8, 10 and 12. These animals had complete obstruction of the common duct without evidence of peritonitis and with no free bile in the peritoneal cavity. Cultures from the peritoneal cavity of two of the animals (dogs no. 10 and 12) were negative. We failed to make cultures from the other two.

Group 2 includes dogs no. 2, 6, 7 and 14 in which there was partial obstruction to the flow of bile, no evidence of infection of the peritoneal cavity and no free bile in the peritoneal cavity. Dog no. 14 was living and in good condition at the end of the observations. The bilirubin content of the blood of this dog was consistently low, indicating that the ligation of one of the hepatic ducts produced only partial obstruction to the flow of bile. In the other three animals, the common duct was ligated at one place only, and at autopsy the obstruction to the flow of bile was found to be incomplete.

Group 3 includes dogs no. 1, 3, 5, 11 and 13, all of which had had the common duct ligated and sectioned, except dog no. 13, which had had a single hepatic duct ligated. These animals had infection of the peritoneal cavity and considerable elevation of the bilirubin content of the blood.

Group 4 includes only two animals (dogs no. 9 and 15). In these dogs there was bile in the peritoneal cavity without evidence of infection. In dog no. 9, the common duct was ligated at two places and sectioned between ligatures, but the proximal ligature came off. In dog no. 15, the common duct was ligated, but not sectioned. At autopsy, however, the common duct was found to be ruptured.

For each of the dogs in the four groups, repeated total and differential white cell blood counts were made, according to the supravital technic, prior to operation. The smallest number of preoperative counts was two (dog no. 2). The lowest number of preoperative counts for the other dogs was four and the greatest twenty-one. The latter were done on dog no. 3, which was given bromsulphalein daily for fifteen days prior to operation. Following operation, daily total and differential counts were made for five consecutive days on twelve of these animals. Of the remaining three animals, one (dog no. 12) had three daily counts and then one count two days later; one (dog no. 9) had four daily counts; another (dog no. 15) had three daily counts. Total and differential counts were made at intervals of from one to two days after the first five days following operation until the animal died or was killed. The greatest number of counts made on any animal after operation was eighteen (dog no. 6). The supravital technic was relied on mainly, but, in a number of instances, fixed preparations were made and stained with Wright's stain. Determinations of the icterus index and of the amount of bilirubin in the blood serum were made at intervals by the van den Bergh method. The highest values were obtained in dog no. 10, in which the icterus index reached a maximum of 31.3 units and the van den Bergh test for bilirubin gave 123.3 mg. per thousand cubic centimeters of blood.

In each of the nine guinea-pigs, the common duct was ligated at one place. Autopsies were always performed at the end of the period of observation, and special attention was paid to the same points that were mentioned in explanation of the procedures for dogs. These nine guinea-pigs were divided into two groups:

1. Group 1 includes guinea-pigs no. 3, 4, 5, 7, 8 and 9, all of which had complete obstruction at the point of ligation, as was shown at autopsy. Guinea-pig no. 9 showed a ruptured gallbladder, but this was thought to have been a terminal event. In none of these animals was there any infection of the peritoneal cavity nor any severe infection in the region of the wound.

2. Group 2 includes guinea-pigs no. 1, 2 and 6, in which there was complete obstruction to the flow of bile and also severe infection. Guinea-pig no. 1 had severe cellulitis of the anterior abdominal wall and localized peritonitis. Guinea-pig 2 had an infection with a gas-producing organism in the left inguinal region and possibly also peritonitis. Guinea-pig no. 6 had an ulcerated area in the region of the wound on the anterior abdominal wall.

The same general plan was followed in establishing the normal total and differential counts for these animals before and after operation, as for the dogs. Determinations of the amount of bilirubin in the blood serum were made in four instances at the time of autopsy. In each case, elevated values were obtained, the highest values being found in guinea-pig no. 5 with an icterus index of 10.8 and a quantitative van den Bergh test showing 27.8 mg. of bilirubin per thousand cubic centimeters of blood. Studies of the blood were made daily on all the guinea-pigs of group 1 for at least five days after operation. Guinea-pig no. 3 had daily blood counts for nine days after operation, this being the longest time after obstruction

of the common duct during which the blood of any guinea-pig was counted. In group 2, guinea-pig no. 1 had daily blood counts for four consecutive days, guinea-pig no. 2 for two days and guinea-pig no. 6 for five days.

In addition to the aforementioned series of fifteen dogs and nine guinea-pigs, two control series of guinea-pigs were studied. The first control series included four guinea-pigs (guinea-pigs no. 10, 11, 12 and 13). The normal total and differential white blood cell counts were established for these animals (as for the previous groups) prior to etherization. They were then subjected to ether anesthesia for thirty minutes, and following this, their total and differential white blood cell values were determined daily for five days.

The second control series (guinea-pigs no. 14, 15, 16, 17 and 18) were operated on under ether anesthesia. In this operation, which occupied thirty minutes, the abdominal wall was opened and the common duct was exposed, but not ligated. In other words, practically all the steps used in ligation of the common duct were carried out. Following operation, total and differential blood counts were made daily for five consecutive days. Autopsies were performed on all the animals of this series, except guinea-pig no. 17, on the eighth day after operation.

RESULTS

All the postoperative average figures here given are for the daily counts made on the five days immediately following operation, except for dogs no. 12 and 15, for which only three daily postoperative counts were made, and dog no. 9, for which there were four daily postoperative counts. This five-day period was used rather than the period until death because it gave a more uniform method of comparing the average blood counts of these animals and, further, because the averages obtained for this period differed but slightly from those obtained by the use of the counts up to death. There was one exception: in group 3, in which the average postoperative total count increase was for this five-day period 77.2 per cent as against 129.6 per cent for the total postoperative period.

The principal observations as regards the white blood cells in the four groups of dogs were as follows:

1. An increase in the total number of white blood cells following operation. This occurred in each group, the greatest increase being in group 3 (131.7 per cent) and the smallest increase being in group 1 (83.1 per cent).

2. An increase in the absolute number of neutrophils in each group, this increase being definitely greater proportionately than that of the total white blood cell count. The greatest rise was in group 4, in which there was an increase of 228.7 per cent. The smallest increase occurred in the animals of group 2 (129.4 per cent).

3. A diminution in the number of eosinophils in the dogs of each group. The greatest decrease occurred in group 4 (87.9 per cent). The next lowest drop occurred in group 2 (55.7 per cent).

4. A slight diminution in the number of lymphocytes in groups 1, 3 and 4, the greatest decrease being found in group 4, in which there was a diminution of 19.8 per cent. Group 2 showed an increase of 54.3 per cent.

5. An increased absolute number of monocytes in groups 1, 2 and 3 but a diminished number in group 4. The rise in group 1 was small (9.9 per cent). The greatest increase was in group 3 (136.6 per cent). In group 2 the rise was 50.5 per cent. The diminution in group 4 was 26.2 per cent.

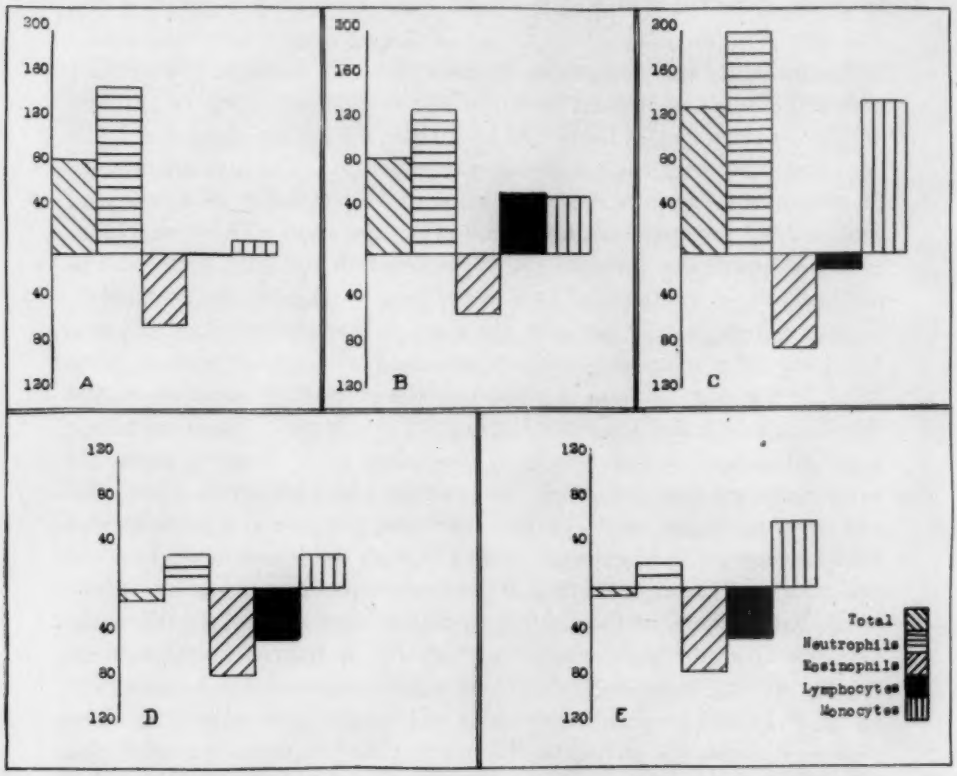
In group 1, the changes in lymphocytes and monocytes were well within the limits of normal variation, the average preoperative absolute number of lymphocytes being 1,643 per cubic millimeter, as against 1,619 per cubic millimeter for the postoperative period. The average number of monocytes prior to operation was 1,876 per cubic millimeter, as against 2,061 per cubic millimeter following operation. There was, however, an appreciable increase (83.1 per cent) in the total count and in the number of neutrophils (147.9 per cent). Again, the eosinophils showed a drop of 62.9 per cent, the average preoperative number being 1,563 per cubic millimeter and the average postoperative number being 580. In the chart, section *A* represents the percentage variations in the blood counts of the animals of group 1. In group 2 there were two main differences in the results as compared with those in group 1; namely, the lymphocytes showed an increase (54.3 per cent) from 1,102 per cubic millimeter to 1,701 per cubic millimeter, and the monocytes were increased (50.5 per cent) from 1,960 per cubic millimeter to 2,950 per cubic millimeter. Section *B* represents the percentage variations in the blood counts of the animals of this group. In group 3, the main deviation from the blood counts in group 1 is an increase in the average number of monocytes from 1,976 per cubic millimeter before operation to 4,675 (136.6 per cent) per cubic millimeter after operation. The greatest increase was in dog no. 13, in which the preoperative average was 1,984 as against 6,656 per cubic millimeter after the operation. Section *C* represents the percentage variations in the white blood cell counts of the animals of this group. In group 4, the only important variation from the counts found in group 1 was a drop of 26.2 per cent in the number of monocytes, the average preoperative count being 2,245 per cubic millimeter and the average postoperative count being 1,657 per cubic millimeter.

Six of the dogs died spontaneously. The remaining nine were killed. The longest period during which any of the animals was kept under observation following operation was twenty-one days (dog no. 6). The shortest period was three days (dog no. 15).

The essential changes in the blood of the guinea-pigs following experimental obstruction to the flow of bile through the common duct were:

1. A slight increase in the number of neutrophils in the presence of a slight decrease in the total number of white cells.

2. An appreciable drop in the number of eosinophils in group 1 (78.4 per cent) and in group 2 (76.2 per cent).



The variations in the numbers of the white cells of the blood in experimental obstructive jaundice: *A*. The average percentage variations from normal in the numbers of the white blood cells of dogs following complete experimental obstruction to the common duct, no peritonitis or free bile being evident in the peritoneal cavity at the time of autopsy (group). *B*. The average percentage variations from normal in the numbers of the white blood cells of dogs following partial biliary obstruction, no peritonitis or free bile being present in the peritoneal cavity at autopsy (group 2). *C*. The average percentage variations from normal in the numbers of the white blood cells of dogs, following operation, peritonitis and jaundice being found at autopsy (group 3). *D*. The average percentage variations from normal in the numbers of the white blood cells of guinea-pigs following complete biliary obstruction without severe infection (group 1 with guinea-pig no. 5 omitted). *E*. The average percentage variations from normal in the numbers of the white blood cells of guinea-pigs following complete biliary obstruction in the presence of severe infection (group 2).

3. A similar but less marked drop in the number of lymphocytes in group 1 (46.4 per cent) and in group 2 (45.3 per cent).

4. An increase in the number of monocytes in both groups. If guinea-pig no. 5 is omitted from group 1, the average increase is 28.5 per cent, but if this animal is included it is 66.5 per cent. In group 2, the increase is 57.8 per cent.

There was no striking difference in the results of the experiments with the two groups of guinea-pigs, except that there was a greater percentile rise of the monocytes in group 2 than in group 1, if guinea-pig no. 5, which showed a different reaction as regards the blood from the other guinea-pigs in this group, is omitted. All the averages given are for the five daily postoperative counts, except in guinea-pig no. 1, which had four daily postoperative counts, and guinea-pig no. 2, which had two daily postoperative counts. Section *D* shows the percentage variations in the blood counts of the guinea-pigs of group 1 (not including guinea-pig no. 5). Section *E* shows the percentage variations in the blood counts of the guinea-pigs of group 2. Guinea-pig no. 9 had a ruptured gall-bladder at autopsy, but this was thought to have been a final accident, since previous autopsies had revealed the likelihood of such an occurrence. Guinea-pig no. 4 had a rather large necrotic area of one of the middle lobes of the liver, suggesting that the arterial blood supply to this area had been cut off.

A comparison of the amount of jaundice and the number of monocytes in the circulating blood showed absolutely no correlation between the two.

There was only one change of any degree among the control animals that were treated with ether anesthesia—namely, an average increase (52 per cent) in the number of eosinophils from 935 to 1,420 per cubic millimeter. These increases in the number of eosinophils were so irregular that it was not thought that they were due to the ether anesthesia, but rather to changes peculiar to the animals. Eosinophilic variations are likely to be great in normal guinea-pigs. The monocytes dropped (22.8 per cent) from 1,214 per cubic millimeter to 937 per cubic millimeter, whereas there was a slight increase (13.1 per cent) in the total white blood cell count and in the absolute number of neutrophils (19.3 per cent). The lymphocytes showed practically no change (2.2 per cent). All these animals were free from gross abnormalities at autopsy, except guinea-pig no. 10, which had an adherent pleura at the left base of the lung.

The second control series of animals, that is, the series consisting of animals that had had an exploratory laparotomy, showed no changes of note in either the total or the differential white blood counts. The greatest change was in the number of neutrophils, which showed an

average increase of 22.2 per cent. The percentile change in the numbers of the other white blood cell constituents of the blood was within a variation of plus or minus 10 per cent.

One of these animals (guinea-pig no. 17) had its ears badly bitten in a fight and later died. No autopsy was performed on this animal, but autopsies were performed on the four remaining ones. In all of them, the wounds of the operations were in excellent condition, and slight, if any, infection was present. The postmortem observations revealed no abnormalities, and cultures from the peritoneal cavities were sterile.

The alterations resulting from obstruction to the flow of bile through the common duct will be described in another communication. Both gross and microscopic changes from normal were noted in the liver. The changes in the livers of the guinea-pigs were much more pronounced than were those in the livers of the dogs.

COMMENT

Increases in the amount of bilirubin in the blood of the dogs with complete obstruction were not associated with equal increases in the number of monocytes in the circulating blood. There was, however, an average increase of 50.5 per cent in the number of circulating monocytes following partial biliary obstruction in dogs. This response to partial obstruction is in entire agreement with the observations of Holt.[4] The explanation of these results offers some difficulty. It would seem that there existed a delicately balanced mechanism, slight jaundice producing monocytosis and severe jaundice causing no change in the number of these cells. Of course, one cannot assume that it is necessarily an accumulation of bilirubin or bile salts that is responsible for the reaction. It may be the cholesterol, the unsaturated fats or other less well known substances. Partial obstruction may cause the production of the optimal amount of this substance, or substances, whereas more marked obstruction may call forth too much of this unknown substance. On the other hand, complete obstruction may result in such a sudden change in the condition in the liver as to prevent the production of this "x" substance. Again, it is possible that partial obstruction may produce its result by changes in organs other than the liver. For example, it is conceivable that partial obstruction may cause changes not only in the functioning of the liver, but in the functioning of the spleen, the bone-marrow or the connective tissues. One certain fact stands out—that jaundice and monocytosis in dogs cannot be related in a quantitative fashion.

The results of the study of the series of guinea-pigs with complete obstruction corroborates the work with the dogs. There is, it is true, an average increase of 28.5 per cent in the number of monocytes in five guinea-pigs with complete obstruction, but this is not a great percentile

change for these animals and, further, the average absolute values in all these animals are within the normal limits, 1,461 per cubic millimeter being the highest average for the five-day period after operation. The highest single value occurred in guinea-pig no. 7 on the third day after operation; this was 2,303 per cubic millimeter. There was distinct uniformity of the results in these five animals, but one other animal (guinea-pig no. 5), with complete obstruction and no infection of the peritoneal cavity, gave a different response. The average monocyte count of this animal prior to operation was 1,185 per cubic millimeter and after operation it was 3,908 per cubic millimeter, a maximal value of 7,091 per cubic millimeter occurring on the fourth day after ligation of the bile duct. This response is so different from that of the other guinea-pigs of this series that it probably represents a different type of reaction. It cannot be stated whether this particular reaction was in the nature of an idiosyncrasy of this guinea-pig or whether it was due to some factor which was not recognized. Certainly, there is no marked response on the part of the monocytes in the blood of dogs or guinea-pigs to the production of jaundice by mechanical obstruction of the common duct.

The changes in the number of white blood cells in the presence of peritonitis in dogs and severe subcutaneous infection in guinea-pigs are of interest. In both animals there was a distinct rise in monocytes with infection. The number of these cells showed an average increase of 136.6 per cent in infected dogs, and of 57.8 per cent in the three infected guinea-pigs. The explanation of a pronounced increase in the number of monocytes in the presence of peritoneal infection remains obscure, but has been noted before by Huffman, Lawrence and Jones.[1] It certainly is not due to leukocytosis per se, since there was an average increase of 83.1 per cent in the total number of white blood cells in the dogs of group 1, in which there was no true increase in the number of monocytes. In the three infected guinea-pigs there was an actual average diminution of 7 per cent in the total number of white blood cells after operation. It may be that only certain types of infection are responsible for this response or possibly only those animals which have been treated in certain ways—e. g., by ligation of the common duct—react in this manner.

Analysis of the changes in the number of white blood cells in each group of animals described in this paper reveals one result that is constant, namely, the diminution in the absolute number of eosinophils. The average diminution for the four groups of dogs and the two groups of guinea-pigs is 74.2 per cent. The lowest average diminution for any one group of animals (55.7 per cent) occurred in the dogs of group 2 and the maximal average diminution (87.9 per cent) in the dogs of group 4. It may be seen, therefore, that the diminution was of about the same range in all these animals. The explanation is not obvious.

Whether it is the bilirubin, the degeneration of the liver, the bile salts, the unsaturated fats, the cholesterol or other factors is unknown. Certain it is that experimental obstructive jaundice in guinea-pigs and dogs produces a marked diminution in the number of eosinophils. That the diminution in the number of eosinophils, in guinea-pigs, at least, is not the result of ether anesthesia or operation is conclusively shown by the two control series of animals. There was actually an increase in the number of eosinophils in both control series of guinea-pigs, which is in contrast with Krumbhaar's [5] observations that in dogs the eosinophils are diminished in number following various surgical operations under ether anesthesia. Chadbourne [6] (1899) found an increase in the number of eosinophils in patients following operations in which ether narcosis was used. Stahl [7] (1921) and Garrett [8] (1928) both found a diminution in the number of eosinophils in persons soon after surgical operations. Foote and Selinger [9] (1927) were unable to find any changes of note in the number of eosinophils in an analysis of 147 postoperative leukocytoses following tonsillectomy. The reports in the literature, therefore, are confusing. It is probable that certain types of operations may produce a drop in eosinophils, whereas others may not. Trauma, infection and necrosis may all play a part. Since all the external conditions of the control and the ligated series of guinea-pigs were as nearly identical as possible, with the exception of ligation in the one group, it would seem that the marked diminution in the number of eosinophils in these animals was in some way associated with the peculiar changes resulting from ligation of the common duct. One cannot assume, however, that these changes were specific, since a diminution was found by us in dogs in other postoperative conditions. The jaundice is probably not an important factor, since patients with jaundice may show an appreciable number of eosinophils, particularly in the presence of pruritus.

There was also a diminution in the number of the lymphocytes in all the animals except the dogs of group 2, in which there was an average increase of 54.3 per cent. The average diminution (25.4 per cent) for the five other groups of dogs and guinea-pigs was much less than the decrease in the number of the eosinophils. Also, the variations in per-

5. Krumbhaar, E. B.: Observations on the Nature of Postoperative Leucocytosis in the Dog, Ann. Surg. **66**:133, 1917.

6. Chadbourne, T. L.: Ether—Leukocytosis, Philadelphia M. J. **3**:390, 1899.

7. Stahl, Otto: Ueber die postoperative Leukozytose, Deutsche med. Wchnschr. **47**:1550, 1921.

8. Garrett, G. H.: Postoperative Changes in the Blood After General and Local Anesthesia, U. S. Vet. Bur. M. Bull. **4**:27, 1928.

9. Foote, J. A., and Selinger, Maurice: Postoperative Leukocytosis and Temperature Variations Following Tonsillectomy: An Analysis of 147 Cases Arranged in Four Age Groups, Am. J. Dis. Child. **33**:96, 1927.

centage change were much greater, there being a decrease of only 0.4 per cent in group 1 of the dogs and of 46.4 per cent in group 1 of the guinea-pigs. With these wide fluctuations, it does not seem that the changes in the number of lymphocytes were of as much significance as those in the number of the eosinophils.

The changes in the total number of white blood cells and neutrophils were constant for the four groups of dogs, showing an increase in each group. These results may, in part, have been due to localized infection. In both series of guinea-pigs, however, the number of neutrophils was increased slightly, but the total number of white blood cells was diminished. The leukopenia may have been due to the more profound disturbances of the organism in the case of the guinea-pig.

CONCLUSIONS

Complete, sudden obstruction to the common duct in dogs and guinea-pigs, in the absence of severe infection, produces only slight increase in the number of monocytes in the circulating blood, whereas partial biliary obstruction in dogs produces a slightly greater increase in the number of monocytes in the blood. Complete or partial sudden obstruction to the common duct in the presence of severe infection in dogs or guinea-pigs is associated with a definite increase in the number of circulating monocytes.

There is a constant and marked diminution in the number of eosinophils in dogs and guinea-pigs with complete or partial experimental biliary obstruction. The operation per se does not explain this response in the guinea-pig.

The response of the lymphocytes to obstructive jaundice experimentally produced in dogs and guinea-pigs is inconstant.

A postoperative neutrophilic leukocytosis occurs in dogs after experimental biliary obstruction, whereas a leukopenia occurs in guinea-pigs after a similar procedure.

EFFECT OF CERTAIN TOXIC SUBSTANCES IN BACTERIAL CULTURES ON THE INTESTINAL MOVEMENT

III. THE EFFECT OF THE PHYSIOLOGICALLY ACTIVE SUBSTANCES OF THE GAS BACILLUS ON THE MOVEMENT OF THE INTESTINE IN THE INTACT ANIMAL *

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In a recent communication, Kendall and Schmitt [1] reported the finding of a physiologically active (histamine-like) substance in filtrates of carbohydrate medium cultures of the gas bacillus which: (1) caused immediate contracture of the isolated strip of intestine of the guinea-pig, and (2) a transient drop of blood pressure when the filtrate was injected into the vein of a dog. The substance was not obtained from culture mediums from which carbohydrate was excluded, but from mediums in which fermentation was active, the substance was present in considerable—nearly maximal—amount in forty-eight hours. The substance was heat stabile and was antagonized successfully by a titration using solution of formaldehyde, which indicates its content of free aromatic ethylamine groups as in histamine. Certain aldehydes known to react with aromatic amines also showed neutralizing effects, while ketones and other aldehydes did not.

These observations led us to the study of this substance or substances in the intact animal by the method recently described by Ecker and Biskind.[2]

METHOD

Two mediums were employed: (1) skimmed milk and (2) sucrose veal infusion Witte peptone broth of *p*H 7.2. Fifty cubic centimeters of each of the

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* From the Institute of Pathology, Western Reserve University.

1. Kendall, A. T., and Schmitt, F. O.: Proc. Soc. Exper. Biol. & Med. **24**:104, 1926. Kendall, A. T.: Ibid. **24**:316 and 493, 1926. Kendall, A. T., and Alexander, H. L.: Ibid. **24**:894, 1926.

2. Ecker, E. E., and Biskind, M. S.: Effect of Certain Toxic Substances in Bacterial Cultures on Intestinal Movement; Effect of Filtrate of Young Cultures of Colon-Typhoid Group of Organisms on Intestinal Movement of Rabbits as Recorded by New Cinematographic Method; Correlation of This Effect with Production of Food Poisoning by Members of This Group, Arch. Path. **7**:204 (Feb.) 1929.

mediums was placed in each of a series of test tubes measuring 20 cm. by 2.5 cm. in order to have a high column and to secure anaerobiasis. The mediums were then inoculated with a strain of the gas bacillus (obtained through the courtesy of Dr. Ivan Hall). The tubes were then placed at 37 C., and the organisms allowed to grow for various periods of time. In the case of the milk cultures, the separated whey was filtered through a Berkefeld N candle, while the broth cultures could be passed directly through the candle. The milk cultures showed stormy fermentations. Prior to the intravenous injection of the filtrates into the animals, the filtrates were carefully neutralized to a p_H of 7 with tenth-normal sodium sodium hydroxide.

The whey control was obtained by clotting the skimmed milk with butyric acid, and neutralizing the acid with tenth-normal sodium hydroxide. The original neutral sterile filtered sucrose broth was used as a broth control in the series of animals into which the filtrates of the sucrose broth cultures were injected.

The preparation of the animals (rabbits) was the same as that described by Ecker and Biskind. As further controls, a series of normal rabbits received the same doses of the filtrates intravenously and their reactions were carefully observed.

EXPERIMENTS

Table 1 shows the effect of the filtered whey from skimmed milk cultures of various ages.

In this series of experiments, six of the nine control rabbits died in prostration or convulsions in eighteen hours or less. Soft stools were obtained in three of the animals, the intestinal reactions being mild as compared with those obtained with filtrates of cultures of the paratyphoid (*aetrycke* type) and *B. enteritidis* group of organisms.

The laparotomized animals into which the whey filtrates of cultures sixty-six hours old were injected showed an increase of rhythmic longitudinal muscle movements (pendulum) with localized circular spasms and filling of the ileum. When, however, the whey filtrates of five day cultures were employed, the pendular movements extended to the duodenum and jejunum. Here, also, localized areas of spasms were noted. The same reactions also occurred with employment of whey filtrates of nine day and fourteen day cultures. The neutral whey filtrate control did not produce noticeable changes.

Table 2 shows the effect of the filtered sucrose broth cultures of various ages.

The control rabbits into which were injected the filtrates of the toxic sucrose broth cultures showed depression, prostration, labored respiration and occasionally soft stools. The symptoms appeared usually in about one-half hour after the injection of the filtrates. All the animals recovered completely within twenty-four hours.

In this series, the laparotomized animals showed marked pendulum movements and localized circular spasms of the duodenum and jejunum when filtrates of twenty-four hour cultures were given by vein. As filtrates of the older cultures were injected (five day cultures), the

TABLE 1.—*Results of Injection of Filtrates of Skimmed Milk Cultures of the Gas Bacillus Into Laparotomized Rabbits*

Age of Culture	Dose,* Cc.	Weight of Rabbit, Gm.	Results**					Weight, Control Normal Rabbit, Gm.	Results in Control Normal Rabbit**
			Duodenum and Jejunum	Ileum	Cecum	Colon	Rectum		
66 hr.	2	2,000	Quiescence	25′: slight increase of pendular motion with localized circular spasm and filling	Quiescence	Quiescence	Quiescence	2,050	1 hr.: soft stool 2 hr.: apparently normal conditions 17 hr.: convulsions and death
96 hr.	1	1,975	Quiescence	32′: slightly increased pendular motion	.....	Slight spasm	40′: expulsion following spasticity	2,100	1 hr.: soft stool; weakness; depression 18 hr.: recovery
5 days	2	1,880	13′: increased pendular motion with filling 20′: localized circular spasm	38′: filling; pendular motion; propulsion 47′: localized circular spasm	50′: mild contractions	.....	60′: expulsion	2,250	52′: partly nodular, partly soft stool 107′: marked symmetric convulsions; opisthotonus; respiratory failure; death
5 days	1.8	2,100	10′-25′: only slight pendular movement†	10′-25′: slight pendular movement	Quiescence	Quiescence	Quiescence	1,680	
5 days	1.8	2,650 (pregnant)	15′: slight pendular movement‡	20′: slight pendular motion	.....	.....	45′: expulsion	.....	10′: hyperexcitability; urination 25′: jerky respiration 45′: prostration 18 hr.: death
5 days	1	1,780	25′: filling; slight pendular movement 32′: circular bands; tendency to propulsion 30′: marked local circular spasm	25′: filling; pendular motion 30′: increased pendular motion 50′: spastic circular areas	Quiescence	Quiescence	Quiescence	1,850	20′: restlessness; labored respiration 45′: prostration 55′: nodular defecation; urination 60′: marked prostration 18 hr.: death
5 days	1	1,900	0′: distention with gas 1′: gas distention causing increased pendular motion 25′-30′: localized circular spasticity; increased pendular motion	15′: slightly increased pendular motion	1′: distention 15′: slight cecal motion	1′: distention 15′: pendular motion	20′: expulsion	2 200	15′: depression 30′: excitability; jerky, rapid respiration 18 hr.: recovery
9 days	2	2,175	27′: increase (slight) of pendular motion	27′: slightly increased pendular motion 52′: occasional filling	.....	67′: marked spasticity	.....	2,080	1 hr.: excitability; defecation; tremors; prostration 18 hr.: convulsions; death
14 days	2¶	1,740	105′: increase (slight) of pendular motion	40′: areas of local spasm; increased pendular motion	Quiescence	Quiescence	60′: expulsion	2,375	40′: depression; respiration jerky 1 hr.: Prostration 18 hr.: death
Control (whey filtrate neutralized with butyric acid)	2	1,875	Quiescence	Quiescence	Quiescence	Quiescence	Quiescence	2,350	Quiescence normal

* All filtrates neutralized to p_H 7 at injections. All injections intravenous.
** Time given is time after injection.
† 45′: animal died on board in asphyxial convulsions.
‡ 30′: rhythmic contraction of uterus; bloody vaginal discharge; death on board in 90 minutes, in asphyxial convulsion.
¶ 1 cc. injected into lumen; no toxic effect.

TABLE 2.—*Results of Injection of Filtrates of Sucrose Broth Cultures of the Gas Bacillus Into Laparotomized Rabbits*

Age of Culture	Dose, Cc.	Weight of Rabbit, Gm.	Results					Weight, Control Normal Rabbit, Gm.	Results in Control Normal Rabbits
			Duodenum and Jejunum	Ileum	Cecum	Colon	Rectum		
24 hr.	2	1,725	2′: marked pendular movement 25′: localized circular spasm	Same as in duodenum	20′: slight contractions	.....	35′: expulsion; contractions	1,850	25′: slight depression 35′: normal conditions 18 hr.: recovery
48 hr.	2	1,930	35′: marked pendular movement; slight filling of ileum; local circular spasm	Same as in duodenum	.....	25′: slight spasm	.....	2,050	35′: slight depression 40′: more marked depression; labored respiration 18 hr.: recovery
72 hr.	2	1,650	60′: filling of entire small intestine; localized circular spasm; increased pendular motion	Same as in duodenum	.....	.....	60′: expulsion	1,600	60′: marked dyspnea 70′: prostration and opisthotonus; seemingly almost near death 18 hr.: recovery
5 days	2	2,000	15′: circular spasm; marked pendular motion in entire small gut, most marked in ileum	15′: localized peristalsis	30′: slight contractions	.....	.....	1,780	20′: slight depression 30′: prostration 18 hr.: recovery 3 days later: death
5 days	3	2,200	16′: increased pendular motion in entire small gut; marked ileac spasticity	Same as in duodenum	.....	50′: slight spasticity	50′: filling with gas	2,000	15′: depression 45′: prostration 18 hr.: recovery
8 days	2	2,460	35′: filling; increased pendular motion 40′: marked filling; pendular motion and peristalsis	35′: increased pendular motion 40′: peristalsis	.....	.....	.....	2,000	25′: depression 45′: prostration 65′: prostration and opisthotonus 18 hr.: recovery
8 days	2	1,600	20′: increased circular spasm 30′: increased pendular motion and peristalsis	20′: increased pendular motion; filling 30′: marked filling; marked peristalsis 55′: mild rush (incomplete)	.....	.....	.....	1,550	20′: depression; labored respiration 40′: prostration 60′: soft stools; continued depression 18 hr.: recovery
Sterile control	2	2,850 (pregnant)	Only slight pendular motion	Practically complete quiescence	.....	.....	.....	2,900 (pregnant)	No effect
5 days	20, by stomach tube	1,800	0′: marked stomach distention of feeding 20′: slight undulations of stomach wall 20′-2 hr.: marked pendular motion; extreme filling; peristalsis and mild rushes	0′: distention by gas partly	0′: distention, by gas partly	.....	.....	2,050	0-2 hr.: apparently normal; nodular defecation

reactions became more marked, and the circular spasms of the upper intestines became pronounced. The lower intestines showed only their usual propulsive movements. The injection of the filtrate of the sterile control sucrose broth produced nothing unusual; the normal pendular motions of the upper intestines were noted here.

Intrastomachal injection (by catheter) of 20 cc. of a filtrate of a five day sucrose broth culture produced marked pendular motions with filling and peristalsis in the upper intestines. In this animal, a partial peristaltic rush was observed. Beyond defecation, nothing unusual was seen in the control animal, which received the same dose of the filtrate by stomach tube.

In both of these series of experiments, little or no abnormality was noted in the reactions of the lower intestines.

In our series of experiments, a minimum of ten minutes elapsed before a noticeable change occurred in the contractions of the intestines in situ. The isolated strips of intestines, as used by Kendall, responded immediately to the addition of the toxic filtrate. From our experiments, therefore, it is difficult to conclude at present whether one or more toxic substances are responsible for the effects noted.

SUMMARY AND CONCLUSIONS

Rabbits into which neutral whey filtrates of from three to nine day old skimmed milk cultures of the gas bacillus were injected showed increased rhythmic longitudinal muscle movements with filling of the duodenum, jejunum and ileum. Localized areas of circular spasms were also seen. A peristaltic rush as described by Ecker and Biskind and seen in rabbits into which filtrates of broth cultures of the paratyphoid-enteritidis group of organisms were injected, was not found.

Rabbits into which filtrates of neutral sucrose broth cultures of the organism were injected showed the same reactions as those into which the toxic whey filtrate was injected, but to a more marked extent.

Control injections of neutral whey or neutral broth failed to produce the reactions.

No abnormal movements were noted in the lower intestines.

Control rabbits receiving the filtrate of the neutral toxic whey became depressed and prostrated, and showed labored respiration usually followed by death with or without convulsion within eighteen hours. The animals appeared excited. The same symptoms of intoxication were seen in rabbits into which the filtrates of the neutral toxic sucrose broth were injected, but the animals survived.

General Review

THE PATHOLOGY OF TETANUS*

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CONDITIONS UNDER WHICH TETANUS MAY OCCUR

The natural home of the tetanus bacillus is probably in the intestinal tracts of man and animals.[1] From these sources it finds its way into the soil, but whether it multiplies in the soil is really uncertain. It probably does under conditions of symbiosis with aerobic micro-organisms that reduce the oxygen tension sufficiently to provide the anaerobic requirements of the tetanus bacillus.

Certainly, the great majority of cases of tetanus arise through wounds contaminated with soil, as in war,[2] Fourth of July injuries,[3] subungual hematomas[4] and deep injuries of various kinds. Tetanus neonatorum[5] is not uncommon, particularly in the tropics; it is generally due to contamination of the umbilical cord. Tetanus sometimes occurs after criminal traumatic abortion,[6] after hemostatic injection of infected gelatin,[7] as a complication in drug inebriety[8] and even as a result of flea bites on the feet.[9] The tetanus bacillus has been found in court plaster,[10] but I have seen no record of tetanus following the use

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1. Noble, W.: J. Infect. Dis. **16**:132, 1915. Ninni, C.: Ann. d'ig. **30**:756, 1920. Dubovsky, B., and Meyer, K. F.: J. Infect. Dis. **31**:614, 1922. Bauer, J., and Meyer, K. F.: Ibid. **38**:295, 1926.

2. Sanford, A. H.: Internat. A. M. Museums Bull. **7**:365, 1918. Cummins, S. L., and Gibson, H. G.: Lancet **1**:325, 1919. Bruce, D.: Ibid. **1**:331, 1919. Churchill, W.: Ibid. **1**:725, 1919.

3. Fourteenth Annual Summary of Fourth of July Injuries, editorial, J. A. M. A. **67**:676 (Aug. 26) 1916.

4. Berard, L., and Lumiere, A.: Presse méd. **32**:621, 1924.

5. Anders, J. M., and Morgan, A. C.: Tetanus Neonatorum, J. A. M. A. **47**:2083 (Dec. 22) 1906. Hill, E. W.: Tetanus, Arch. Int. Med. **8**:747 (Dec.) 1911.

6. Schneider, G. H.: Centralbl. f. Bakteriol. (Ref.) **87**:222, 1927.

7. Anderson, J.: Hygienic Laboratory Bulletin, no. 9, 1902.

8. Doane, J. C.: Tetanus as a Complication in Drug Inebriety, J. A. M. A. **82**:1105 (April 5) 1924.

9. Rohardt, W.: Centralbl. f. Bakteriol. (Ref.) **87**:222, 1927.

10. McCoy, G. W.; Leake, J. P., and Corbitt, H. B.: Pub. Health Rep. **32**: 1450, 1917.

of court plaster. A few cases of tetanus following extraction of teeth have been recorded,[11] and I once recovered the tetanus bacillus from the mouth of a healthy child.[12]

A number of cases of tetanus have followed smallpox vaccination, due, in some of the earlier instances before adequate methods of controlled manufacture were in vogue, to contaminated viruses,[13] to the use of bunion pad dressings[14] and to careless contamination of the vaccination sore by the patient himself. Francis,[15] Geiger[16] and others have shown that the danger of tetanus following vaccination with good virus, properly applied and cared for, is practically negligible.

Tetanus following surgical operations always presents an interesting problem because the question generally arises as to the source of the organisms, whether from catgut or from the intestinal tract of the patient. Thus, Jaffe[17] found anaerobic bacilli in a case of tetanus following an ovariotomy, but, in England, was unable to make animal tests. Huggins[18] pointed out that while "catgut has been looked on with a good deal of suspicion, there are few cases in fact where it (tetanus) has been definitely traced to catgut" and urged the view that the intestine is the real origin in many cases. Patton,[19] on the contrary, held that suture material is the common source of postoperative tetanus and observed that there is no record of a case of tetanus complicating typhoid fever. Neither is there any record of tetanus following submucous resection of the nasal septum, which would seem to exclude air as a possible source of the organism. It certainly seems plausible that poor catgut might serve as a source of *B. tetani,* but I am inclined to concur with Huggins that it does so only rarely now. The temptation to blame the catgut in a case of postoperative tetanus is well illustrated in Dyke's case following cesarean section,[20] in which catgut from the same lot gave negative results. I believe that the facts in this case indicate that tetanus bacilli from the intestinal tract of the patient became localized in the sutures after operation.

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11. Maranon, G., and Velarde, J.: Abstr., Dental Cosmos **67**:231, 1925; abstr., J. Bact. **9**:271, 1925.
12. Hall, I. C.: J. Infect. Dis. **37**:87, 1925.
13. McFarland, J.: J. M. Research **7**:474, 1902.
14. Armstrong, C.: Pub. Health Rep. **40**:1351, 1925; **42**:3061, 1927; Postvaccination Tetanus and Its Prevention, J. A. M. A. **90**:738 (March 10) 1928.
15. Francis, E.: Hygienic Laboratory Bulletin, no. 95, 1914.
16. Geiger, J. C.: California State J. M. **15**:152, 1917.
17. Jaffe, J. I.: Brit. M. J. **1**:1480, 1909.
18. Huggins, R. R.: Surg. Gynec. Obst. **30**:142, 1920.
19. Patton, W. D.: Canad. M. A. J. **13**:332, 1923.
20. Dyke, S. C.: Lancet **2**:596, 1926.

Tetanus occurs naturally in man, in the horse [21] and in the camel,[22] and it can be reproduced experimentally in mice, rats, guinea-pigs, rabbits, fowls, goats and other warm-blooded animals. But there is considerable difference in susceptibility among these, and cold-blooded animals are insusceptible. Knorr [23] showed that weight for weight the susceptibility of horses is twice that of goats, thirteen times that of mice, 2,000 times that of rabbits and 200,000 times that of fowls. It also takes about ten times as much tetanus toxin to kill a rat weighing 150 Gm. as to kill a guinea-pig weighing 350 Gm.

INVASION OF THE TISSUES BY BACILLUS TETANI

Bacillus tetani possesses little ability to invade tissues in the body distant from the portal of entry, i. e., a wound usually, though Lacy and Murdock [24] recorded a rare case in which the organism was recovered from the cerebrospinal fluid. Growth is dependent on anaerobiosis, which is favored by anemia and necrosis, traumatic or otherwise. Frequently in wounds the presence of aerobic bacteria serves to favor anaerobic growth by reduction of the oxygen tension, and certainly tissue cells that have been deprived of their usual oxygen supply through the circulation may do so. Vaillard and Vincent [25] found that although *B. tetani* grows well at from 20 to 22 C., sporulating freely, it forms little or no toxin at that temperature, and such cultures can be injected into animals in considerable quantities without injury.

Cultures grown at 37 C., on the other hand, were pathogenic in minute doses, owing to the powerful soluble toxin, but when heated to 65 C. for twenty minutes they too became impotent in animals. Vaillard and Vincent [25] discovered that detoxified spores were reactivated by lactic acid, trimethylamine, *"Microbacillus prodigiosus"* or even simple trauma. Vincent [26] further showed that guinea-pigs inoculated with tetanus spores detoxified by heating to 85 C. for three hours, and exposed for one-half hour at 40 C., during which the animals' temperature might rise to 42 C. or more, succumbed to tetanus, while similarly inoculated control animals, not so exposed, suffered no harm. Tarozzi [27] found that detoxified tetanus spores might be demonstrated in experimental animals as long as three and a half months after their inocula-

21. MacConkey, A. T.: Brit. J. Exper. Path. **7**:133, 1926.

22. Rabagliati: J. Comp. Path. & Therap. **33**:10, 1920.

23. Knorr, A.: München. med. Wchnschr. **45**:321 and 362, 1898.

24. Lacy, G. R., and Murdock, C.: J. Lab. & Clin. Med. **7**:100, 1921. Montesano, G., and Montessori, M.: Centralbl. f. Bakteriol. **22**:663, 1897.

25. Vaillard, L., and Vincent, H.: Ann. de l'Inst. Pasteur **5**:1, 1891.

26. Vincent, H.: Ann. de l'Inst. Pasteur **8**:450, 1904.

27. Tarozzi, G.: Centralbl. f. Bakteriol. 1, O. **40**:305 and 451, 1906.

tion, but Canfora [28] was able to confirm Tarozzi's observations only up to fifty-five days. In 1911, Semple [29] added quinine to the list of reactivating agents, and in 1914 Francis [15] showed that the "washing of tetanus spores by successive suspension and centrifugalization in large quantities of saline solution did not rid them of their toxin," and that tetanus spores detoxified by heating to 80 C. for one hour previous to injection might be reactivated by quinine or staphylococci up to one month in guinea-pigs and by staphylococci but not by quinine up to four months in mice.

There seems to be a marked difference in the persistence of pathogenic spores and nonpathogenic spores in the tissues of animals. Koser and McClelland [30] observed that the spores of nonpathogenic aerobes disappeared rapidly from the site of inoculation and from the viscera, while those of *B. tetani* and some other anaerobes were still present after several weeks or even months. Teale and Bach,[31] in 1920, found that the washed spores of various aerobic bacilli, including *B. anthracis,* did not usually remain latent in the animal body, many being rapidly ingested and destroyed by phagocytes, while others vegetated and were more slowly destroyed. *B. tetani* and *B. welchii* behaved similarly except that a small, sometimes a large, proportion did not germinate but remained latent; multiplication of washed anaerobic spores rarely occurred in the tissues. Teale and Bach found that lactic acid, ferric chloride, calcium chloride and oleum phosphoratum (B. P.) given subcutaneously up to four days after the organisms, and gelatin, charcoal or peptone given intraperitoneally with the organisms favored infection.

In 1919, Bullock and Cramer [32] showed that surface cultures and washed broth cultures in *B. tetani, B. welchii, Vibrion septique* (*B. septicus*) and *B. oedematiens* (*B. novyi*) were noninfectious for mice and guinea-pigs. Such inactivated suspensions could be reactivated by the readdition of culture fluid in amounts too small to have any effect alone on animals, which suggests the presence of Bail's aggressins.[33] Certain ionizable salts of calcium, such as the chloride, nitrate or acetate, had a similar effect when injected either at the same time, or previous to,

28. Canfora, M.: Centralbl. f. Bakteriol. 1, O. **45**:495, 1908.

29. Semple, D.: Scientific Memoires of Officers of the Medical and Sanitary Departments of the Government of India, 1911, no. 3; quoted by Francis (footnote 15).

30. Koser, S. A., and McClelland, J. R.: J. M. Research **37**:259, 1917-1918.

31. Teale, F. H., and Bach, E.: J. Path. & Bact. **23**:315, 1919-1920.

32. Bullock, W. E., and Cramer, W.: Proc. Roy. Soc., London (series B) **90**:513, 1917-1918.

33. Bail, O.: Centralbl. f. Bakteriol. 1, O. **27**:517, 1900; **33**:343, 610 and 756, 1902; **40**:371, 1906.

or within a few days after, the injection of the organisms. Insoluble salts of calcium, such as the carbonate, and the chlorides of sodium, potassium, ammonium and magnesium were ineffective. Strontium chloride was active with *Vibrion septique,* but only in larger doses; citrates given simultaneously with calcium ions rendered the latter innocuous, presumably by precipitation. Aqueous extracts of earth were often potent, but not always in proportion to the calcium content. Direct contact between the spores and the calcium was unnecessary; positive results were obtained when injections were made at the same time into different sites, or at different times into the same or different sites.

The action of the calcium salts was on the tissues of the body, making them more favorable for the growth of the bacteria. For when toxin-free spores were suspended in a solution of calcium chloride, then centrifugated out and injected, they had not become virulent. Neither did administration of calcium chloride to the animals render them more susceptible to the action of injected toxins. But if the organism and the calcium chloride were injected separately, the disease localized where the calcium was introduced.

Bullock and Cramer designated this phenomenon as "defense rupture," or "kataphylaxis," and interpreted the distribution of tetanus and gaseous gangrene in the great war as an expression of the varying calcium content of the soil in different localities. The experimental facts also help to explain the occurrence of latent and delayed tetanus, as well as the occasional relapses following apparently successful use of antitoxin.[34] Russell [35] found that tetanus spores vegetate in the tissues only in the presence of necrosis, due for example, to trauma, earth or calcium chloride. According to Fildes,[36] the failure of inoculated toxin-free spores to germinate is not due to phagocytosis but to the presence of oxygen in the normal tissues. Necrotizing agents permit vegetation and toxin production by lowering the oxygen tension, i. e., by producing anemia in the tissues.

THE ACTION OF TETANUS TOXIN

I may now discuss what happens when the tetanus bacillus, having found lodgement in the tissues and conditions suitable for multiplication produces its toxin. First of all, it is rare for the organism to penetrate undamaged tissues, although it should not be forgotten that associated bacteria such as streptococci, staphylococci and others may do so. Perhaps, some of the failures in the therapeutic use of tetanus antitoxin

34. Whittemore, W. L.: Tetanus, J. A. M. A. **71**:1995 (Dec. 14) 1918.
35. Russell, D. S.: Brit. J. Exper. Path. **8**:377, 1927.
36. Fildes, P.: Brit. J. Exper. Path. **8**:387, 1927.

are due to lack of appreciation of the fact that other bacteria often find a foothold in the body at the same time as *B. tetani* and may cause death in spite of the protective action of the antitoxin. But the tetanus bacillus itself generally remains localized and it is the absorption of toxin from the localized focus which causes the disease. Obviously, débridement of the focus is one of the most important items both in prevention and in cure.

Ehrlich [37] distinguished two antigenic poisons in tetanus toxin, i. e., tetanolysin, which dissolves red blood cells in vitro, and tetanospasmin, which is responsible for the symptoms of tetanus. There is no evidence that tetanolysin is of any consequence in the natural or the experimental disease, and it may not even be produced by some strains under certain conditions. Thus, in 1912, I was producing potent tetanus toxins (from 10,000 to 20,000 minimal lethal doses per cubic centimeter) [38] which were absolutely nonhemolytic, yet the antitoxins resulting from the immunization of horses with them were fully protective against the test toxin supplied from the U. S. Hygienic Laboratory, which was actively hemolytic in vitro.

Nerve tissue has a marked affinity for tetanospasmin, as was demonstrated by Donitz [39] and by Wassermann and Takaki.[40] But this affinity is by no means peculiar to nerve tissue, Peterson [41] having shown some degree of neutralization of tetanus toxin by leukocytes and fixed tissue cells of different organs of various animals such as the dog, rabbit and guinea-pig. It may be that variation in the combining abilities of the various tissues in different animals accounts in part for the marked difference in susceptibility to tetanus that is known to exist.

There have been much speculation and experimentation as to the route followed by tetanus toxin from the place of its elaboration to the site of damage. Many observations have shown that intravenous inoculation of tetanus toxin leads to generalized tetanus, while subcutaneous or intramuscular inoculations lead to localized tetanus. Zupnik [42] distinguished between tetanus descendens and tetanus ascendens, the former being attributed to the supposed absorption of toxin by the central nervous system, particularly the spinal cord, from the circulating blood, the latter to direct absorption of the toxin by the muscles. Thus tetanus descendens would manifest itself by generalized symptoms;

37. Ehrlich, P.: Berl. klin. Wchnschr. **35**:273, 1898.
38. Hall, I. C.: Univ. Calif. Pub. Path. **2**:97, 1913.
39. Donitz, W.: Deutsche med. Wchnschr. **23**:428, 1897.
40. Wassermann, A., and Takaki, T.: Berl. klin. Wchnschr. **35**:5, 1898.
41. Peterson: Ztschr. f. Immunitätsforsch. u. exper. Therap. (Orig.) **8**:498, 1910.
42. Zupnik, L.: Wien. klin. Wchnschr. **15**:89, 1902.

tetanus ascendens, by localized symptoms. Trismus and opisthotonos, which are often so conspicuous in human tetanus, were regarded as symptoms of tetanus descendens, and explained by the theory that the muscles of the neck and back are most strikingly affected because they are so much stronger than their respectively opposing groups.

Vaillard and Vincent [43] in 1890 showed that the contractions of a particular muscular area ceased when the motor nerves leading to it were severed, and in 1892, Brunner [44] found that there was apparently no direct action of tetanus toxin on muscles isolated from their ganglionic centers. Bruschettini [45] in the same year demonstrated the presence of tetanus toxin in both the central and the peripheral nervous systems after subcutaneous inoculation. Milchner,[46] Marie [47] and Wassermann and Takaki [40] all showed that the toxins combined chemically with nervous tissues, as may be demonstrated by the protective action of the latter in animals inoculated with mixtures of toxin and brain substance. These observations led Marie and Morax [48] and Meyer and Ransom [49] independently to discover that the toxin is absorbed by the myoneural junction and passes to the spinal nerve centers by way of the axis cylinders of the motor nerves. Ransom [50] subsequently reiterated this view and emphasized that "the cells of the central nervous system do not pick up the toxin from the blood or the lymph; the only route by which the cells can be attacked is via the motor nerves. The sensory nerve trunks are not implicated in the transport of toxin from the seat of injection or the blood stream to the central nervous system. Nevertheless, the sensory cells are susceptible if the toxin is brought into direct contact with them. Injection into a posterior root does not cause any muscular rigidity, but there is extreme hyperaesthaesia in the sensory areas corresponding to the injected roots." Meyer and Ransom [49] called this "tetanus dolorosus."

There is no question that tetanus toxin often enters the circulatory blood stream. In the early days of serum manufacture, before suitable safety tests such as are now required had been devised, a number of deaths from tetanus in St. Louis were ascribed to tetanus toxin presumably present in the blood of a horse which supplied diphtheria

43. Vaillard, L., and Vincent, H.: Semana méd. **10**:425, 1890.

44. Brunner, C.: Berl. klin. Wchnschr. **28**:881, 1891; Deutsche med. Wchnschr. **20**:100, 1894.

45. Bruschettini, A.: Riforma med. **8**:256, 1892.

46. Milchner, R.: Berl. klin. Wchnschr. **35**:369, 1898.

47. Marie, A.: Ann. de l'Inst. Pasteur **11**:591, 1897; ibid. **12**:91, 1898.

48. Marie, A., and Morax: Ann. de l'Inst. Pasteur **18**:818, 1902.

49. Meyer, H., and Ransom, F.: Arch. f. exper. Path. u. Pharmakol. **49**:369, 1903.

50. Ransom, F.: Lancet **2**:928, 1917.

antitoxin.[51] Bailly asserted that he had confirmed a case of acute spontaneous tetanus in a rabbit by inoculation of a guinea-pig with 3 cc. of the rabbit's blood, the guinea-pig also developing tetanus, and suggested the utilization of heart's blood from cadavers in proving the cause of death in suspected tetanus, but Cesari was never able to produce tetanus in mice with the blood of horses showing symptoms of tetanus while undergoing immunization.[52] While these observations seem to be contradictory to those of Bolton and Fisch,[51] they are really not so, for the latter showed that the toxin disappeared from the blood stream before, or coincidently with, the appearance of symptoms; Bailly's idea of diagnosing tetanus by inoculation of animals with blood secured post mortem is therefore valueless.

Teale and Embleton [53] held that "although tetanus toxin ascends to the central nervous system by way of the axis cylinders of the nerves, it also to a very great extent passes up the nerves to the cord by way of the perineural lymphatics. Blocking of the latter paths greatly delays and in some cases completely blocks the occurrence of tetanus in the part corresponding to the nerve whose lymph path has been blocked.

"Although tetanus toxin passes rapidly from the blood vessels into the connective-tissue spaces and thence to the thoracic duct, the toxin does not pass from the capillaries of the central nervous system to the tissues thereof." Neither does it pass from the choroidal plexus to the cerebrospinal fluid. It is perhaps important that, "although bacteria can pass through the posterior root ganglion to the cord, colloidal pigments and tetanus toxin are prevented from doing so. Iodine, although it prevents tetanus toxin from producing its characteristic effects when iodized toxin is inoculated subcutaneously or intravenously, does not affect the toxin when inoculated intracerebrally; it does not hinder the occurrence of the typical symptoms of cerebral tetanus, and there is no apparent diminution in its toxicity.

"Tetanus anti-toxin does not pass to the central nervous system either by way of the blood vessels, axis cylinders, or neural lymphatic channels. It also cannot pass from the cerebrospinal fluid when inoculated intra-thecally into the substance of the cord. The antitoxin simply acts by combining with the circulating toxin, and that at the seat of production, and prevents it from reaching the central nervous system. The toxin already in this position is unaffected." Thus, the use of antitoxin in man, if not wholly preventive, often permits the development of localized tetanus.[54]

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51. Bolton, B. M., and Fisch, C.: Tr. A. Am. Phys. **17**:462, 1902.

52. Bailly, G.: Bull. Soc. Med. Vet., 1925; abstr., Bull. de l'Inst. Pasteur **24**:31, 1926.

53. Teale, F. H., and Embleton, D.: J. Path. & Bact. **23**:50, 1919.

54. Burrows, H.: Lancet **1**:139, 1917.

After the toxin reaches the spinal cord, its further diffusion, according to Ponomareff,[55] may proceed either by the nerve substance or by the cephalo-arachnoid fluid, diffusion by the latter vehicle supposedly accounting for the rapid development of generalized symptoms of tetanus following localized tetanus in some cases. Ponomareff supported this view by an ingenious experiment in dogs in which the subarachnoid space in the brain was separated from that of the cord by a muscular ring reducing the freedom of circulation of the fluid. Animals so treated and inoculated in one of the hind legs always developed symptoms of generalized tetanus from ten to thirty hours later than did untreated controls similarly inoculated. Similarly, in normal inoculated dogs in which the anterior movement of cephalo-arachnoid fluid from the cord to the brain was accelerated by repeated withdrawal of fluid from the brain the symptoms of generalized tetanus appeared from eight to fifteen hours earlier than in the untreated controls.

LESIONS IN TETANUS

The literature dealing with this phase of the subject is scanty and somewhat conflicting. In natural tetanus, the primary wound may vary from a bee sting to a comminuted fracture with deep lacerations. The resulting secondary infection may be so slight as to involve almost no marked local reaction or it may be so severe because of secondary infections as to result in gaseous gangrene. In the so-called "idiopathic" tetanus, it may be impossible to detect the primary lesion, particularly if it is hidden in the viscera, and "there are no clinical features of a wound pathognomonic of tetanus infection."

The marked antemortem rigor of tetanus disappears at once on death, and sometimes even a few moments before death; on the other hand, there is some evidence that the usual postmortem rigor develops more rapidly following tetanus, possibly due to the saturation of the muscles with the products of their extreme activity, but of course, such rigor has no significance in the diagnosis of tetanus at autopsy.

When one performs an autopsy on guinea-pigs dead of experimental tetanus, one rarely sees any macroscopic lesion except a slight congestion at the site of inoculation in material from which it is usually impossible to stain micro-organisms or to recover cultures; the viscera are practically always normal to the naked eye, with the exception of slight pulmonary congestion in occasional instances.

Stangl[56] found that guinea-pigs into which pure cultures of *B. tetani* had been injected in sufficient quantity to produce symptoms within twelve hours revealed at that time an intense cellular invasion

55. Ponomareff, A. W.: Compt. rend. Soc. de biol. **97**:503, 1927

56. Stangl, F. H.: J. Infect. Dis. **31**:22, 1922.

which sharply defined the affected area, but which never led to definite necrosis or abscess formation, although from 80 to 90 per cent of the cells were polymorphonuclear leukocytes, the remainder being mononuclear leukocytes and large mononuclear wandering cells. Stangl noted that the capillaries were engorged and the endothelial cells enlarged in the area surrounding the point of inoculation. Most of the bacilli were observed in the spaces between the leukocytes and the fixed cells, but a few were found within the leukocytes. At this stage there was neither hyaline nor waxy change in the muscle fibers, but the nuclei of the sarcolemma were swollen.

In older lesions, the polymorphonuclear leukocytes became less numerous while lymphocytes and mononuclear wandering cells increased to one third or one half of the cells present. Still later (from five to six days) large fibroblasts and giant cells were present, suggesting a reparative phase of the reaction.

Stangl also noted disappearance of the striations in the muscles, granular disintegration of the nuclei and a well defined waxy degeneration. Microscopic changes similar to those observed in guinea-pigs were also seen in a local lesion studied post mortem in a case in man. It would be interesting to confirm these results and compare the action of toxin with that of whole cultures.

Marinesco [57] found hemorrhages in the gray matter of the cords of guinea-pigs dead after an injection of tetanus toxin. The ganglion cells had also become smaller and more fusiform. The cell plasma was more than ordinarily granular and failed to show the usual differentiation on staining. When the convulsions had lasted for some time, the nucleus was said "to be ill defined and to stain more intensely than usual," which sounds like a contradictory statement. The medullated nerve fibers were also found to be degenerated in such cases. Hunter [58] found similar hyperemic changes in the cords of two human victims, with altered ganglion cells, but failed to find them in a third case, undoubtedly tetanus, since the bacillus was cultivated from the wound. Hunter considered the hyperemia of the cord to be a nonspecific action of the toxin.

Goldscheider and Flatau [59] observed certain characteristic changes in the motor cells of the anterior horns in experimentally tetanized rabbits depending in the order of their development on the concentration of toxin injected and the duration of the disease. These were best displayed by Nissl's stain, and consisted primarily in an enlargement of the

57. Marinesco, G.: Gazettes méd., Paris, July 11, 1896; quoted by Hunter (footnote 58).

58. Hunter, W. K.: Brit. M. J. **2**:333, 1927.

59. Goldscheider, A., and Flatau, E.: Fortschr. d. Med., 1897, 1898; quoted by Moschcowitz (footnote 64).

nuclei, which at the same time became less distinct, followed by an enlargement and disintegration of Nissl's cell and granules, and an enlargement of the whole cell. Therapeutic use of antitoxin had a distinct retarding influence on these changes. They subsequently verified these observations in the spinal cord of a human victim of tetanus, and essentially similar results are said to have been obtained by Matthes,[60] Westphal,[61] Goebel[62] and Tauber.[63] Moschcowitz[64] considered that these changes are "characteristic of tetanus and are constantly found." One may well agree with him that "our present knowledge of the pathogenesis of tetanus points with great probability to the anterior horns of the spinal cord as the primary seat of origin for the tetanic contraction." It is clear from this why the period of incubation in tetanus is shorter and death comes sooner when the path from lesion to cord is short, as Kairinkschtis[65] and others have noted.

Nelson[66] recently observed in a single case that the changes usually observed in the cells of the anterior roots of the cord may also be seen in those of the posterior roots, particularly at the level of the fifth lumbar segment, and suggested, on the one hand, that the toxin might be transmitted by the nerve fibers of the sensory root as well as by those of the motor root, or, on the other, that diffusion of the toxin might proceed by the perineural lymphatics outward from the cord so as to injure the cells of the posterior root ganglion, in which case the maximal degree of injury in the posterior root ganglion of the fifth lumbar segment might be correlated with a maximal concentration of toxin at the level at which the toxin entered the cord.

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60. Matthes, P.: Deutsche Ztschr. f. Nervenh., 1898; quoted by Moschcowitz (footnote 64).

61. Westphal, A.: Fortschr. d. Med., 1898; quoted by Moschcowitz (footnote 64).

62. Goebel, W.: Monatschr. f. Psychiat. u. Neurol., 1898; quoted by Moschcowitz (footnote 64).

63. Tauber, A. S.: Wien. klin. Wchnschr., 1898; quoted by Moschcowitz (footnote 64).

64. Moschcowitz, A. V.: Ann. Surg. **32**:219, 1900.

65. Kairinkschtis, W.: Ztschr. f. Hyg. **95**:220, 1922.

66. Nelson, S. H.: Lancet **2**:852, 1926.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths.—Thorburn Brailsford Robertson, professor of biochemistry and general physiology in the University of Adelaide, has died of pneumonia at the age of 45.

M. Fernan-Nunez, a graduate of the University of Madrid in 1925, has been appointed director of the department of pathology and bacteriology in Marquette University, Milwaukee.

George W. Bachman, formerly of the school of hygiene and public health of Johns Hopkins University, is now professor of parasitology in Columbia University, with duties in the school of tropical medicine, University of Porto Rico.

Stuart Graves, dean and professor of pathology in the school of medicine of Alabama University, has resigned as acting state health officer.

David R. Briggs has been appointed as assistant professor of chemistry in the department of pathology of the University of Chicago.

I. S. Falk has resigned as professor in the department of hygiene and bacteriology, University of Chicago.

In the school of medicine of the University of Illinois, George Milles and Louis Parmacek have been appointed instructors in the department of pathology and bacteriology, and A. J. Nedzel instructor in the department of bacteriology and preventive medicine.

Robert Muir, professor of pathology in the University of Glasgow, has been awarded a Royal medal by the Royal Society of London in recognition of his work in immunology and experimental pathology.

A department of medical and surgical research has been established in the Ohio State University, with Charles A. Doan of the Rockefeller Institute for Medical Research as chairman.

Robert W. Lamson has been appointed associate professor of bacteriology and immunology in the University of Southern California.

David H. Kling has accepted a Frederick Brown fellowship in orthopedic research at the Hospital for Joint Diseases in New York.

Milton G. Bohrod has been appointed pathologist to the Decatur and Macon County Hospital, Decatur, Ill.

William K. Hueper, associate professor of pathology in Loyola University and pathologist to Mercy Hospital, Chicago, has been appointed pathologist to the Oncologic Hospital in Philadelphia.

William Royal Stokes, professor of bacteriology, University of Maryland, and city bacteriologist, Baltimore, has died from parrot fever contracted from handling infected parrots, at the age of 60 years.

Cancer Research.—The University of California now has an endowment of $200,000 for research in cancer and allied subjects.

The fund for cancer research at the graduate school of medicine of the University of Pennsylvania has received $210,000 from an unnamed donor. The director of the fund is Ellice McDonald, who is also chairman of a board of directors of research. A central laboratory has been established, with departments for tissue culture, for experimental cancer in animals, and for the study of problems in radiation (in cooperation with the Bartol Research Foundation). The plans also include the development of a complete anticancer center at the American Oncologic Hospital, and of research on the biochemistry and immunology of cancer at the Philadelphia General Hospital. Grants have been made for work on the metabolism of cells (W. D. Bancroft, Cornell University), on the fixation of pathologic material (Henry J. Fry, New York University), on the sensitization of cells to fluorescent substances and roentgen rays (Eric Ponder, New York University), and on the quantitative spectographic estimation of substances in biologic material (Andrew Dingwall, Columbia University).

University of Cambridge Studentships.—1. Gwynaeth Pretty Studentship, the holder of which shall devote himself to original research in the etiology, pathology and treatment of disease, with particular but not exclusive reference to those diseases which cripple or disable in childhood or early life, is of the annual value of £200 and is tenable for three years.

2. John Lucas Walker Studentship, the holder of which shall devote himself to original research in pathology, is of the annual value of £300 and is tenable for three years.

Applications for these studentships, accompanied by copies of papers containing published work, testimonials and references, should be sent before July 1, 1930, to Prof. H. R. Dean, Department of Pathology, University of Cambridge, to whom also applications for further information regarding the studentships may be addressed.

The International Association for Geographic Pathology.—In 1928, Max Askanazy presented a plan for a coordinated study of pathologic conditions which show geographic variations and for the organization of an international association for that purpose. The project was favorably received by European pathologists, and Max Askanazy, Ludwig Aschoff, Gustav Roussey and Joselin de Jong constituted themselves a voluntary bureau to organize the proposed association. One pathologist from each of different countries was invited to represent his country on an international commission and to organize in his country a national committee to carry on such investigations and collect such data as may be appropriate to the problems under consideration.

Representatives from several countries held an informal meeting in Vienna, in April, 1929, and arranged plans for the ensuing year. Cirrhosis of the liver was selected as the first subject for a geographic study. The bureau has announced that the first formal meeting of the commissioners will be held at Geneva in the late summer of 1931. At that time the report on cirrhosis will be presented and the formal organization of the association completed.

National committees have now been formed in the following countries: Argentine, Austria, Baltic Provinces, Belgium, Brazil, Bulgaria, Canada, Central America, Czechoslovakia, Denmark, England, Finnland, France, Germany, Greece, Holland, Hungary, Italy, Japan, Jugoslavia, Lettland, Lithuania, Lower India, Norway, Poland, Portugal, Roumania, Russia, South Africa, Spain, Sweden, Switzerland, Turkey and the United States. V. H. Moon, of Philadelphia, was chosen by the bureau as the representative for the United States. D. J. Davis, of Chicago, Wiley D. Forbus, of Baltimore, Ernest M. Hall, of Los Angeles, Howard T. Karsner, of Cleveland, Leo Loeb, of St. Louis, David Marine, of New York, Frank L. Menne, Portland, V. H. Moon, of Philadelphia, and Frederic Parker, Jr., of Boston, constitute the national committee for the United States.

Status of British Hospital Pathologists.—According to the *British Medical Journal*, the following recommendations concerning hospital pathologists have been submitted for inclusion in the Hospital Policy of the British Medical Association: That every hospital having at least 200 beds should maintain its own pathologic department. When several hospitals exist in one area it may be sufficient to maintain between them a common department; that the department should be under the direction of a fully qualified medical practitioner who has had special training in pathology; that the pathologist in charge should be regarded as having a status similar to that of other members of the visiting staff; that the hospital work should be the first care of the pathologist; that in return for the performance of the hospital work the hospital should (*a*) pay a fixed salary to the pathologist in charge of the department, and (*b*) bear the full cost of the maintenance of the department and of such a staff, qualified and unqualified, as may be necessary for the efficient work of the hospital; that in suitable circumstances the pathologist in charge be permitted private practice as a consulting pathologist, and allowed to do private laboratory work in the hospital by agreement with the governing body.

Death of Benjamin Roman.—Benjamin Roman, pathologist to the Buffalo General Hospital and research professor of pathology in the University of Buffalo, died of pneumonia, at the age of 53. A few days after his death his widow died, also of pneumonia. Dr. Roman was born in Lithuania but was educated in this country and graduated from Cornell University Medical College in 1903. He spent many years in Europe and studied pathologic anatomy in Vienna and then at the German University in Prague, where he was assistant for several years until the United States entered the War. In 1919 he was chief pathologist to the American Zionist Unit in Palestine, and in 1921 he came to Buffalo. He was an accomplished pathologic anatomist and published results of thorough studies on the portal of entry of the tubercle bacillus, on diseases of the hematopoietic organs, on canine distemper and on other topics. In Buffalo he took an active interest in the *Bulletin of the Buffalo General Hospital*, and he was particularly influential in the staff conferences.

BENJAMIN ROMAN, M.D.

DOCTORATES IN HUMAN AND ANIMAL BACTERIOLOGY AND PATHOLOGY CONFERRED BY AMERICAN UNIVERSITIES, 1928-1929

Callie Hull and Clarence J. West, Research Information Service, National Research Council, Washington, D. C.

California: Oscar Brown Williams, "Studies on the Heat Resistance of Bacterial Spores."

Chicago: Janet MacFarlane Bourn, "Incidence of Pfeiffer's Bacillus in Throats During Epidemic and Interepidemic Periods in Chicago." Graeme Alexander Canning, "Preciptin Reactions with Various Tissues of *Ascaris lumbricoides* and Related Helminths." George William Stuppy, "The Production and Prevention of Pneumonia and Other Pneumococcus Infections: Experiments on the Rabbit and on Monkeys *(Macacus rhesus* and *Cebus capucinus)*." Adah Elizabeth Verder, "Effect of Diets Deficient in Vitamin A or B on Resistance to Paratyphoid-Enteritidis Organisms."

Columbia: Richard Warner Linton, "Mobilization and Transfer of Clasmatocytes." Gonzalo Palacios de Borao, "An Epidemiological Study of Leprosy in Porto Rico with Special Reference to Topographic and Climatic Factors."

Cornell: Georges Abdallah Knaysi, "The Cytology and Microchemistry of Mycobacterium Tuberculosis." Ruth Alice Boak, "The Etiology and Diagnosis of Undulant-Fever in the United States."

Kansas: Louis H. Bally, "Studies in Experimental Anaphylaxis." Clara Nigg, "Studies on Isohemagglutination."

Minnesota: Hilding Cornelius Anderson, "Studies of the Effects of Surgical Reduction of the Renal Tissue." Leone McGregor, "The Finer Histology of the Normal Glomerulus and the Changes that Occur in Glomerulonephritis."

New York: James Franklin Yeager, Jr., "Studies in Hemolysis."

Northwestern: William Walter Brandes, "Studies on the Effect of Mechanical Constriction of the Hepatic Veins with Special Reference to the Coagulation of Blood."

Pennsylvania: Mary Jardine Evans, "A Study on *Hemophilus influenzae*."

Stanford: Paul Jay Beard, "Studies on the Adaptation of the Bacteriophage."

Wisconsin: Frances Elizabeth Holford, "The Placental Transmission of Foreign Protein in Rabbits."

Yale: Frederick William Fabian, "The Influence of Cations upon Bacterial Viability at Various Hydrogen Ion Concentrations." Edward Winfield Morrison, "Selected Properties and Responses of Bacterial Spores."

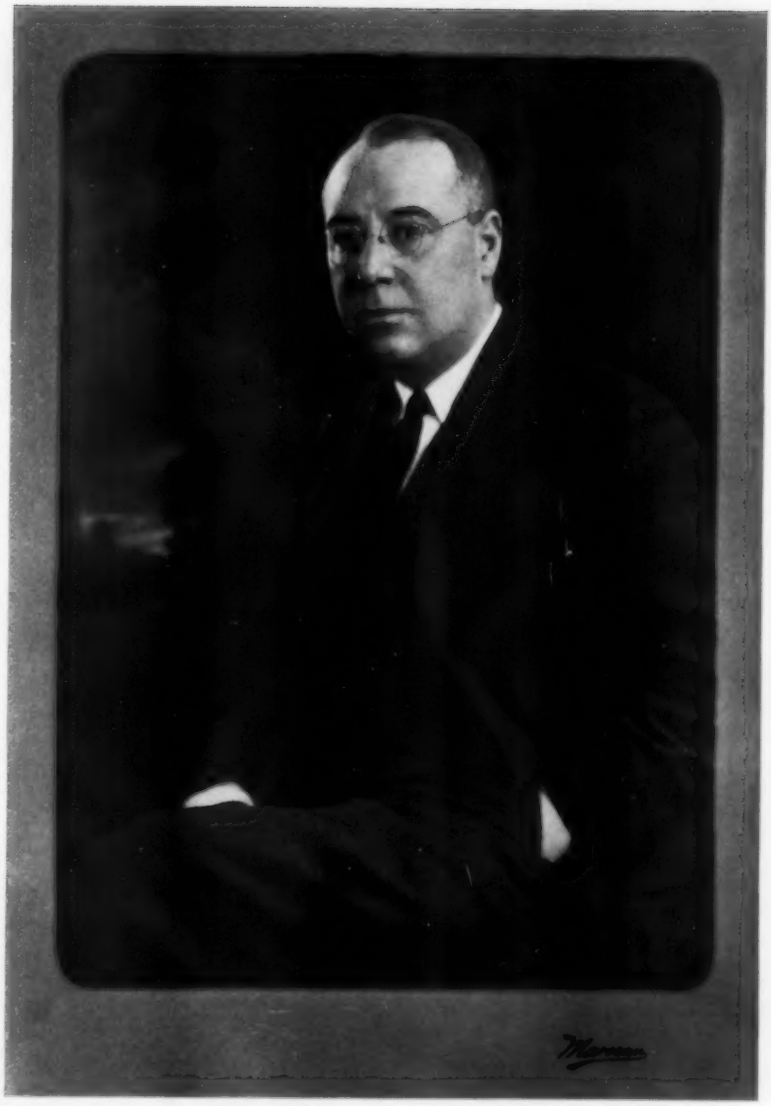
Obituary

RICHARD MILLS PEARCE, JR., M.D.

1874-1930

Richard Mills Pearce, Jr., was born of American parents in Montreal, Canada, March 3, 1874. His family moved to Boston, where he completed his preliminary education at the Boston Latin School. He was graduated from the Harvard Medical School in 1897 with the degree M.D. The honorary degree Sc.D. was conferred on him by Lafayette College of Easton, Pa., in 1915. From 1896 to 1899, he was with Mallory at the Boston City Hospital and was then with Councilman at the Harvard Medical School for one year, after which he headed the remarkable group of young men appointed by Flexner when the latter occupied the chair of pathology at the University of Pennsylvania. During part of 1901 and 1902, he worked at Leipzig with Marchand, and in 1903 he became professor of pathology and bacteriology at Albany Medical College, director of the Bender Hygienic Laboratory and director of the Bureau of Pathology and Bacteriology of the New York State Department of Health. In 1908, he accepted the chair of pathology, originally established by Welch, at University and Bellevue Hospital Medical College, New York. In 1910, he was called to the University of Pennsylvania for the newly created chair of research medicine which was later given the name of the man in whose honor it was endowed, John Herr Musser. Ricketts was appointed professor of pathology at about the same time, but died a martyr before he could assume his new duties. At this juncture, Pearce consented to occupy both chairs until a new professor of pathology could be appointed. At the end of a year, Allen J. Smith returned to the chair of pathology, which he had relinquished to establish a department of tropical medicine. In the later years of Pearce's incumbency in the chair of research medicine, he made numerous surveys of foreign medical education for the Rockefeller Foundation, and in 1920 he became director of the Division of Medical Education of the Rockefeller Foundation. During the Great War, he was in charge of the correlation of medical research in the Council of National Defense, with the rank of major, M.C., U. S. Army, and became the first chairman of the Division of Medical Sciences of the National Research Council.

Pearce was a member of many of the important medical and biological societies. He was president of the American Association of



RICHARD MILLS PEARCE, JR., M.D.
1874-1930

UNIV. OF MICH.

Pathologists and Bacteriologists in 1912 and of the American and Canadian Section of the International Association of Medical Museums in 1914. He was the leader of a group which established the American Society for Experimental Pathology in 1914 and was its first president. In 1915, he was a vice-president of the American Association for the Advancement of Science. In 1904, only seven years after graduation, he was elected a member of the Association of American Physicians. In 1909, he delivered a Harvey lecture, "Problems of Experimental Nephritis," and in 1920 was Hitchcock lecturer at California, where he delivered a remarkable series of five lectures on the subject, "Research in Medicine."

Sturdy and robust in appearance and with great physical energy, he was nevertheless handicapped by a thrombosis of the femoral vein incident to typhoid fever. In 1926, he had the first symptoms of cardiac disease, and in the early autumn of 1929 he had symptoms and signs of myocardial infarction. His abrupt death on Feb. 16, 1930, was due to coronary disease and extensive infarction.

Pearce's research work was always based on concrete problems, from the period of his early work on pneumonia and diphtheria, through that on necrosis of the liver, renal disease and function of the spleen. To the solution of these problems, he brought an imagination sane and well controlled, but always constructive. The attack might be anatomic, histologic, physiologic, chemical, bacteriologic, immunologic or clinical, or any possible combination of these, but methods were no barrier to the exploration, for Pearce had a comprehensive grasp of them all. If technic was to be learned, he learned it, or if he delegated it to an associate, he supervised and criticized the work so that he always shared the responsibility.

Extraordinary devotion to the enlargement of the field of knowledge by research never interfered with his activities in teaching. On the contrary, it appeared to bring him to his classes with an ever refreshed enthusiasm. His lectures were models of order and clarity, and the brevity with which he presented a full discussion of a given topic was unparalleled. He introduced to this country the utilization of the methods and results of experimentation for large classes of students. He had a genuine interest in all his students, but gave particular attention to the welfare of the gifted ones. At Pennsylvania, this was shown in a material way by the establishment of a chapter of a national medical fraternity and a chapter of Alpha Omega Alpha honorary medical fraternity. His pupils occupy important posts in universities and hospitals throughout this country, and it is noteworthy that two chairs at the University of Pennsylvania are now occupied by men who received much of their training and stimulus from Pearce.

Pearce's studies of the philosophy of education as applied to medicine resulted in numerous important publications on the subject. With a background of history and philosophy, he brought to these problems scrupulous analysis and thoughtful consideration, which resulted in clear, logical and convincing documents. Their value was reflected not only in his university work, but more broadly in the advice which he was able to give and the projects in the inauguration of which he played a part as an officer of the Rockefeller Foundation.

A natural reserve of manner never submerged his quiet geniality. His broad vision, reinforced by a ready sense of humor, and a reasoning tolerance overbalancing an impatience at waste or indirection brought a convincing sympathy to his consideration of problems and projects. His straightforward arrival at conclusions led to statements at once brief, clear and indubitably sincere. In his publications, he showed in the more general articles a fluent and attractive style and in his scientific communications an astonishing clarity and conciseness. In both, he showed his appreciation of the precise use of words and the refined beauties of the English language. Fond of the open air and the glories of nature, devoted to family and home, his life was well balanced. The strength and fineness of his character were reflected in his entire mode of living, especially in the genuine joy of his work. Duty and service were his doctrine, and he himself exemplified the precept which he quoted from Pasteur, "Work can be made into a pleasure, and *alone* is profitable to a man, to his country, to the world."

H. T. K.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE VELOCITY OF THE BLOOD FLOW IN HEALTH AND DISEASE. S. WEISS, G. P. ROBB and H. L. BLUMGART, Am. Heart J. **4**:664, 1929.

A technic is described by which the velocity of the blood flow may be measured by estimating the difference between the reaction times of histamine at the site of intravenous injection and in the vessels of the face and brain. A markedly prolonged circulation time was always associated with severe circulatory failure, but the reverse was not always true. The velocity of the blood flow was studied in a considerable variety of pathologic conditions and was found to be an important diagnostic aid in differentiating certain diseases associated with dyspnea and edema.

PEARL ZEEK.

THE INFLUENCE OF CERTAIN IRON OXIDES ON THE BLOOD. C. A. DOAN, F. R. SABIN and C. E. FORKNER, Am. J. M. Sc. **117**:201, 1929.

Certain iron compounds (Fe_3O_3 and $Fe_2O_3 \times H_2O$) administered to normal rabbits and to those suffering from anemia after hemorrhage produce definite depression of hemopoiesis and are probably disadvantageous therapeutically in clinical cases of secondary anemia.

PEARL ZEEK.

THE EFFECT OF COMBINED POTASSIUM IODIDE AND THYROID SUBSTANCE UPON THE THYROID GLAND. S. H. GRAY and J. RABINOVITCH, Am. J. Path. **5**: 485, 1929.

Feeding of potassium iodide to normal guinea-pigs stimulates the thyroid gland, whereas feeding of thyroid substance produces the opposite effect. In feeding potassium iodide and thyroid concomitantly, the effect of the former is evidenced by the increased size of the epithelium, and the effect of the thyroid substance is manifested by the hardness of the colloid and the diminished number of mitoses. Preliminary feeding of potassium iodide interferes only slightly with the subsequent depressive action of thyroid substance, and similarly a preliminary feeding of thyroid substance affects only to a small extent the subsequent stimulative effects produced by the feeding of potassium iodide.

AUTHORS' SUMMARY.

THE INFLUENCE OF SUPRARENAL CORTEX AND MEDULLA ON THE GROWTH AND MATURITY OF YOUNG CHICKS. A. G. EATON, W. M. INSKO, G. P. THOMPSON and F. E. CHIDESTER, Am. J. Physiol. **88**:187, 1929.

In groups of young chicks which were fed with desiccated suprarenal cortex and medulla, respectively, in addition to standard rations, it was found that with the feeding of medulla, initial growth rate was unchanged for the first three weeks, after which time the chicks showed less rapid growth. Those fed with cortex showed an early marked retardation of growth, lasting for about eight weeks, but at the end of that time they began to grow more rapidly, and quickly gained until at the end of eleven weeks' observation they almost equalled the controls. Using testicular weight as a criterion, males receiving desiccated cortex matured more rapidly, while those receiving medulla were less mature than control animals.

H. E. EGGERS.

THE INFLUENCE OF DESICCATED SUPRARENAL CORTEX AND MEDULLA ON THE GROWTH AND MATURITY OF YOUNG RATS. F. E. CHIDESTER, A. G. EATON and G. P. THOMPSON, Am. J. Physiol. **88**:191, 1929.

With young rats fed on desiccated suprarenal cortex or medulla in addition to standard diet, it was found that growth was retarded by both, the greater retardation occurring with the cortex. Young females fed with the cortex reached sexual maturity sooner than did the controls or the animals fed on medulla. As males were not tested independently with older females, it was not determined whether these reached sexual maturity before the corresponding females.

H. E. EGGERS.

THE PERMEABILITY OF THE PLACENTA OF THE RAT TO GLYCERINE, ALANINE AND UREA. J. M. LUCK and E. T. ENGLE, Am. J. Physiol. **88**:230, 1929.

Following the subcutaneous injection of glycerin, alanine and urea into pregnant rats, subsequent determinations of these substances showed that the rates of increase of these in the maternal muscle and in the whole fetus were very similar, indicating not only that the placenta is very permeable for these substances, but that the mechanism of absorption by these tissues from the respective plasmas is apparently identical. Very rapid absorption was found of the amino-acids by the liver, apparently with a mechanism of absorption quite different from that operating in muscle.

H. E. EGGERS.

PHYSIOLOGY OF THE CORPUS LUTEUM. W. M. ALLEN and G. W. CORNER, Am. J. Physiol. **88**:340, 1929.

Rabbits were deprived of both ovaries in the eighteenth hour of pregnancy, and the progestational proliferation of the endometrium was maintained by the daily administration of corpus luteum extracts; in these circumstances the embryos survived and grew normally, with normal implantation. In the absence of this induced progestational proliferation, the embryos did not survive beyond the fourth day. These observations are interpreted as certain evidence that the corpus luteum is an organ of internal secretion, having for one of its functions the production of a hormone which induces the special state of the uterine mucosa without which the free blastocytes lack essential protection or nourishment.

H. E. EGGERS.

OBSERVATIONS ON THE FUNCTION OF THE GALL BLADDER. B. HALPERT and M. T. HANKE, Am. J. Physiol. **88**:351, 1929.

Following the oral or intravenous administration of methylene blue (methylthionine chloride, U. S. P.), the dye appears in the bile, and the authors describe a colorometric method for its measurment here. The pigment appears promptly, within a few minutes after its intravenous injection. The quantity in the bile rises sharply to its maximum in about one hour, after which it declines gradually. In bile removed from the gallbladder six hours after injection, there is from two to twenty-two times as much of the dye as is found in corresponding samples from the common duct. At times the concentration of methylene blue in the gallbladder is considerably greater than is ever found in the bile leaving the liver. Since the dye is not excreted by the gallbladder, its increased concentration there is explained on the basis of a slower rate of absorption there than that of the bile. Also, the writers believe that ordinarily bile does not leave the gallbladder via the cystic duct.

H. E. EGGERS.

DIABETES INSIPIDUS—THE DIURETIC SUBSTANCE. H. BOURQUIN, Am. J. Physiol. **88**:519, 1929.

A diuretic substance has been demonstrated in dogs with experimental diabetes insipidus, which is not found in the urine of normal dogs. Such a substance has also been demonstrated in extracts of large amounts of the mammillary bodies and thal-

amus of the brains of normal animals, and is not found in any appreciable quantity in other parts of the brain. Both diuretic substances are destroyed by strong alkaline solutions at room temperature, are destroyed by ashing, are not dissolved by ether, acetone or 95 per cent alcohol, are precipitated by barium hydroxide from somewhat alkaline solution and are not precipitated by phosphotungstic acid. From their similarities in these respects, it may be inferred that they are identical.

H. E. Eggers.

Hyperinsulinism: Report of Two Cases. Frank N. Allan, Arch. Int. Med. **44**:65, 1929.

Hyperinsulinism due to overproduction of insulin from a tumor of the islands of the pancreas is now established as a disease entity. It is probable that hyperinsulinism may also be due to a functional disturbance of the pancreas. The differential diagnosis of hypoglycemia due to hyperinsulinism and hypoglycemia due to selective hepatic insufficiency is a difficult clinical problem. Two criteria may have value in differentiation: the effect of epinephrine hydrochloride and solution of pituitary, and the amount of sugar required to maintain the blood sugar level. When the hypoglycemic tendency is so strong that the patient is incapacitated, surgical treatment appears to promise relief. Three cases are described in which there was a constant tendency to severe hypoglycemia attributed to hyperinsulinism. In case 1, there was a carcinoma of the islands of Langerhans. In case 2, surgical exploration revealed a normal appearing pancreas. Resection of a part of the pancreas was followed by considerable relief. In case 3, in which medical treatment alone was given, the patient is still under observation.

Author's Summary.

Toxic Cirrhosis of Liver Due to Cinchophen. Herbert S. Reichle, Arch. Int. Med. **44**:281, 1929.

Forty-seven cases of cinchophen toxicosis have been published. Ten deaths have resulted. In all cases there is evidence of serious damage of the liver. Every patient who receives cinchophen should be observed for gastro-intestinal symptoms, rashes or icterus, and the occurrence of such symptoms should be the immediate indication for stopping the use of the drug. The therapeutic use of cinchophen may well be reevaluated in reference to its harmful properties.

Author's Summary.

Constitutional Variation and Susceptibility to Disease. Wade H. Brown, Arch. Int. Med. **44**:625, 1929.

So far as they go, my experiments not only are in harmony with known facts concerning human constitution and susceptibility to disease, but they enable one to state some of the general principles of the constitutional concept in simple terms of present knowledge and to visualize conditions which may influence susceptibility to disease. Constitution thus becomes a concrete reality which lends itself to measurement and test in accordance with the demands of modern science. The elementary conception of constitutional variation and its relation to disease, which I have attempted to outline, involves only one assumption, and that is that all functional activities of the body are either performed or controlled by organs and tissues, and that the organs are provided in such numbers and amounts as are necessary for the performance of their appointed functions. One need not know the function of a single organ in order to show that persons differ from one another in respect of their organic equipment, or that they are persons and not standard machines or standard mediums for the growth of pathogenic microorganisms. It can be shown that variations in the mass and mass relations of organs are constantly occurring in response to demands made by changing conditions of life and that these variations in organic constitution are accompanied by variations in chemical constitution, all of which may well be confined within the

usual limits of normal, for they are normal. It can also be shown that these differences and variations in physical and chemical constitution are associated with differences and variations in functional activity and susceptibility to disease or in the degree of natural immunity. Changing conditions of life affect individuals and groups, but as individuals differ in respect of their inherent constitutional equipment, they differ also in their reaction to influences of all kinds. Some are capable of immediate and complete adjustment and others are slow to respond or are incapable of adjustment, so that when the members of a group are subjected to a change in the conditions of life or are exposed to infection under favorable or unfavorable conditions, the response obtained varies according to the capacities of the individual. Hence, even now, there is some understanding of how and why one person differs from another in respect to the general property of susceptibility to disease and why it is that the susceptibility of persons and of populations is not fixed but varies from time to time, independent of any immunity that may be acquired through previous exposure to a given disease. When one is able to base all experiments on material of known genetic constitution and thus link together the two factors of heredity and environment, one will be in a position to gain a much clearer understanding of these intricate problems.

AUTHOR'S SUMMARY.

THE EFFECT OF MECHANICAL CONSTRICTION OF THE HEPATIC VEINS, WITH SPECIAL REFERENCE TO THE COAGULATION OF BLOOD. W. W. BRANDES, Arch. Int. Med. **44**:676, 1929.

A method of mechanically constricting the hepatic veins in the dog has been described. This procedure permits a study of changes occurring in the blood following removal of the liver from, and its return to, the circulation. Following this constriction there is a precipitate fall in blood pressure of from 40 to 60 mm. of mercury, a level which is then maintained reasonably constant for twenty minutes or more. A decrease in the concentration of the blood (an average of 11 per cent in six dogs) with a gradual increase in concentration occurs until, at the end of fifteen minutes, the normal value is approximately reached. A rapid decrease in the blood sugar (average of 42 per cent) is obtained during constriction for fifteen minutes with a rapid rise after release. A definite decrease in coagulation time of from 25 to 50 per cent is observed during constriction, followed by an increase on release. There was a slight decrease of fibrinogen (11 per cent) during constriction and a definite increase of 25 per cent or more on release of constriction. The platelets were slightly decreased (15 per cent) during constriction with slight change on release. Changes in blood calcium can be accounted for by dilution. The experimental results reported indicate that the chief factors, the interaction of which is concerned in the changes in coagulation time during and after constriction of the hepatic veins, are: alterations in antithrombin (herparin) content; increase in the hydrogen ion concentration, and numerical changes in platelets.

AUTHOR'S SUMMARY.

DIABETES IN TWINS. W. STANLEY CURTIS, J. A. M. A. **92**:952, 1929.

Only seven instances of diabetes in twins are on record. To these six are now added, making a total of thirteen. The existence of diabetes in twins in some cases almost simultaneously points to an hereditary background and offers a good field for the investigation of diabetes as a problem in heredity. When diabetes develops in a twin one should consider the other potentially diabetic, particularly if the two are homologous, and any undue strain on the carbohydrate metabolism should be guarded against.

The recognition of eight twins (four sets) with diabetes in a series of 6,000 diabetic patients, when compared with the estimated number of twins in such a group, suggests a larger portion of diabetes in twins (1 to 9) than is the case in

single individuals. It is to be hoped that others who have had similar cases will report them, in order to confirm or disprove these meager data.

AUTHOR'S SUMMARY.

CELL PROLIFERATION RESPONSE TO SULFHYDRYL IN MAMMALS. F. S. HAMMETT and S. P. REIMANN, J. Exper. Med. **50**:445, 1929.

These experiments establish the fact that the sulfhydryl group is stimulative of cell proliferation in mammals as in lower organisms. The fact that the stimulation is exhibited in such a wide diversity of species including both plants and animals is justification for the belief that it is the expression of a fundamental biologic phenomenon.

AUTHORS' SUMMARY.

STUDIES OF TISSUE MAINTENANCE: PERSISTING BLOODLESSNESS AFTER FUNCTIONAL ISCHEMIA. H. P. GILDING and PEYTON ROUS, J. Exper. Med. **50**: 471, 1929.

In regions of the skin which have been bloodless for some time, as a result of the functional readjustments following a reduction of the blood bulk, the ischemia persists long after the blood volume has been restored and the systemic blood pressure has mounted to the initial level or a higher one. The significance of this is briefly discussed.

AUTHORS' SUMMARY.

THE FINAL RESPONSE OF THE SMALL CUTANEOUS VESSELS. PEYTON ROUS and H. P. GILDING, J. Exper. Med. **50**:489, 1929.

A study of the blanchings (Bier's spots) which develop in human skin deprived of circulation has proved them referable to the same general causes that lead to ischemic patching of the skin of animals, and that they are conditioned by the same factors. Both are expressions of a secondary contraction of vessels that have become hyperirritable owing to an inadequate circulation. The contraction is favored by emptying the vessels, but it occurs pronouncedly even when there is a trickle through them of arterial blood. In the case of man the contractile impulse is sometimes so great as to overcome the maximum pressure that the vessels will support. The significance of the observations is discussed.

AUTHORS' SUMMARY.

THE LIVER AS THE SOURCE OF FIBRINOGEN. D. R. DRURY and PHILIP D. MCMASTER, J. Exper. Med. **50**:569, 1929.

In hepatectomized rabbits a progressive decrease in blood fibrinogen occurs. Partial defibrination in the liverless rabbit invariably results in a progressive decrease in blood fibrinogen preceded by a temporary and slight rise. No evidence has been secured of fibrinogen regeneration in the absence of the liver. From this it follows that the liver is the essential source of fibrinogen and in all probability the sole one.

AUTHORS' SUMMARY.

A MECHANISM OF CONSERVATION IN THE KIDNEYS OF THE WINTER FROG. JEAN OLIVER and ESHREF SHEVKY, J. Exper. Med. **50**:601, 1929.

A method of conservation has been demonstrated in the kidneys of winter frogs. The mechanism of this conservation is an increase in the absorptive function and a decrease in the excretory activity of the tubular epithelium. The excessive absorptive process may be depressed by various means. Such a depression in the tubular activity is followed by large increases in the rate of excretion of water, salts and, if present in the urine, phenolsulphonphthalein. Further evidence is thus obtained which supports the theory that phenolsulphonphthalein is excreted chiefly through the glomeruli.

AUTHORS' SUMMARY.

TESTS WITH VARIOUS FOODS IN SPRUE. CHARLES WEISS and O. COSTA MANDRY, J. Immunol. **16**:283, 1929.

An investigation was made to determine whether the untoward gastro-intestinal reactions observed in patients with sprue (diarrhea, tympanites, flatulence, etc.) after eating certain types of food might be of the nature of specific hypersensitiveness. A careful survey was made of the foods commonly eaten by the people of Porto Rico and representative types were selected for cutaneous tests. These include proteins prepared from rice, beans, pork, cod-fish, cocoanut, etc., sugars (saccharose and fructose), fats and oils (lard, butter, etc.), starches prepared from rice, potatoes, beans, etc., and local spices and coffee. The results were clearly negative and indicate that the untoward digestive symptoms in patients with sprue are not due to any specific sensitization to any food products.

AUTHORS' SUMMARY.

THE ACTION OF AUSTRALIAN SNAKE VENOMS ON PLAIN MUSCLE. C. H. KELLAWAY, Brit. J. Exper. Path. **10**:281, 1929.

All the Australian elapine venoms tested have a stimulant action on isolated plain muscle. The type of action resembles the anaphylactic reaction of the isolated plain muscle of the guinea-pig in its latent period, and in the ease with which the muscle is desensitized by the venoms of this group. The Australian venoms produce the reaction in varying concentrations. After reaction to one venom the plain muscle is insensitive to equivalent doses of the other venoms in the group. After desensitization the muscle does not recover its sensitiveness to snake venom, but its reactions to other stimuli are unimpaired. The plain muscle of guinea-pigs sensitized by the injection of egg albumin, after desensitization with snake venom, retains unimpaired its sensitiveness to its specific anaphylactic antigen. After desensitization with egg albumin the muscle appears to be somewhat less sensitive to snake venom. Experiments with ergotoxin suggest that the effect of the venoms is a direct one on the plain muscle. The venoms cause contraction of the isolated uterus of the rat, and the reaction of the plain muscle of the guinea-pig and the rabbit is therefore not due to the production of histamine, as this drug causes relaxation, not contraction, in the uterus of the rat. The reaction differs from that caused by the toxin of *Vibrion septique,* and after desensitization with snake venoms a good reaction can be obtained with this toxin. The behavior of the only two other venoms tested (those of *Naia tripudians* and *Vipera russelli)* is quantitatively widely different from those of the Australian elapines. The stimulant principle in the Australian venoms is moderately thermolabile, and is destroyed at from 92 to 94 C. at about the same rate as the neurotoxic principle. Like the neurotoxic principle, it appears to reside in the proteose fraction of the venom. At pressures of from 300 to 400 mm. of mercury, and during a period of some hours, it only passes with difficulty through pyroxylin filters permeable to erythrodextrins but not to egg albumin or hemoglobin. The stimulant principle is neutralized by antivenin, but the results obtained by titration, using the isolated plain muscle, are quantitative widely different from those obtained by subcutaneous injection in guinea-pigs. Death-adder and tiger-snake antivenins give some protection against Australian venoms other than those against which they are prepared, and nonspecificity of the same order is observed in tests with the isolated plain muscle.

AUTHOR'S SUMMARY.

TETHELIN AS A TISSUE-CULTURE MEDIUM. K. C. RICHARDSON and E. S. HORNING, Australian J. Exper. Biol. & M. Sc. **6**:137, 1929.

The growth-promoting qualities of tethelin have been confirmed in vitro. Cultures of intestinal epithelium from a seven-day embryo chicken in a medium of chick plasma, embryonic extract and tethelin or chick plasma and tethelin, give more extensive proliferation than do similar cultures in plasma and embryonic extract, membrane formation taking place after twenty-eight hours' incubation in the former but not in the latter cultures.

AUTHORS' SUMMARY.

EFFECT OF VITAL STORAGE ON OXYGEN CONSUMPTION OF THE KIDNEY. H. OONK, Beitr. z. path. Anat. u. z. allg. Path. **79**:756, 1928.

Gross, using the Warburg technic for determining cellular respiration, found that the presence of fat and glycogen in morphologic form within the liver cells of the mouse did not increase the oxygen consumption of such tissue, an indication that the fat and glycogen were inert in cellular metabolism. Oonk studied the effects of the vital storage of colloids on the cellular respiration of the kidney by the same technic. The acid vital dyes, trypan blue, lithium carmine and vital red, caused at first a slight increase in oxygen consumption, after which the oxygen intake returned to normal. The basic dye, neutral red, caused no change in tissue respiration. The early increase in oxygen consumption in the case of the acid dyes is due to the fact that the union of such dyes with the protoplasm in vital storage is an active metabolic process. After the dye has united with the protoplasm its presence has no effect on cellular metabolism. Because iron has been supposed to be important in intracellular metabolism, the effect of vital storage of saccharated iron oxide and of ferric citrate was also studied. Neither compound caused any change in tissue respiration, indicating that they are inert in intracellular metabolism, but indicating also that their presence does not depress cellular activity.

O. T. SCHULTZ.

THE ABSORPTION AND EXCRETION OF SULPHUR BY THE SKIN. R. STIGLER, München. med. Wchnschr. **76**:1795, 1929.

Sulphur in ointments applied to the scalp is absorbed and to some extent is excreted by the skin of the entire body in the form of hydrogen sulphide.

AUTHOR'S SUMMARY.

LYMPHATIC DRAINAGE OF CEREBROSPINAL SUBARACHNOID SPACE. G. IWANOW, Ztschr. f. d. ges. exper. Med. **64**:356, 1929.

Iwanow studied the course of lymphatic channels draining the subarachnoid space by following the paths of removal of india ink which had been injected subdurally into dogs. He claims that the particulate matter is removed fairly rapidly and in relatively large amounts from the cranial cavity by means of lymphatics which carry the material by rather direct routes to the cervical lymph nodes and to the lymphoid tissue aggregations of the mucosa of the upper air passages. The mucosal lymphoid follicles he considers important elements for the excretion of metabolic and other waste products derived from the brain. He disagrees with Weed, in that he ascribes only a minor rôle to the pacchionian granulations. These, according to Iwanow, remove the particulate matter used in his experiments only slowly and in small amounts. The paths of removal of the material from the spinal arachnoid space could be less clearly followed. Some of the material is undoubtedly carried upward to the cisterna at the base of the brain, its further fate being the same as that of the carbon particles injected directly into the cranial subdural space. Some of the material was found in the retroperitoneal lymph nodes, in lymphatic channels of the mesentery and in Peyer's patches of the ileum. For the lymphoid tissue of the intestine he postulates an excretory function from the spinal subarachnoid space, although he was unable to trace the continuous pathways.

O. T. SCHULTZ.

EFFECT OF EXPERIMENTAL HYPERTHYROIDISM AND HYPOTHYROIDISM ON GASTRIC HUNGER CONTRACTIONS. A. KRATINOFF, Ztschr. f. d. ges. exper. Med. **64**:376 and 397, 1929.

The frequent occurrence of gastro-intestinal disturbance in clinical hyperthyroidism led to the study of the effects of experimentally produced hyperthyroidism and hypothyroidism on the gastric hunger contractions of dogs. The

hyperthyroid state was brought about by a single 1 Gm. dose of desiccated thyroid in twenty-four hours, by similar amounts of the same material daily over periods up to thirty days and by the intravenous injection of thyroxin. Gastric or duodenal contractions or both were studied by means of a balloon introduced through a permanent gastric or duodenal fistula. Desiccated thyroid caused an increase in the amplitude and frequency of the hunger contractions, led to the interpolation of contractions between the regular ones and increased the tonicity of the empty stomach. Thyroxin had the same effects, leading to the conclusion that the effects of desiccated thyroid were the specific ones of the contained thyroxin. In animals fed desiccated thyroid over a period of thirty days, cumulative effects were noted and alterations in the hunger contraction rhythm persisted for several months after administration of the material was stopped. Two of six dogs did not show the changes described. On the basis of the experimental observations, the thyroid is held to be a factor in maintaining the normal periodicity of gastric hunger contractions. The hypothyroid state was brought about in two dogs by thyroidectomy, the parathyroids and their blood supply being spared. Cachexia and death of the animals occurred after seven and eleven months, respectively. In these animals, the hunger contractions were also increased in amplitude and frequency during the stage of cachexia. The increased gastric motor activity, which is ascribed to the trophic skin lesions present, was associated with ravenous appetite, in spite of which, however, the cachexia was progressive. The latter state is held to be the result of faulty resorption and assimilation from the intestine, due to trophic disturbances in the mucosa.

O. T. SCHULTZ.

CORPUS LUTEUM AND AMENORRHEA. G. A. WAGNER, Zentralbl. f. Gynäk. **52**: 10, 1928.

The function of the corpus luteum consists in the pregravid preparation of the endometrium and the preservation of the status through the prevention of a hemorrhage in the hyperemic mucosa. The menstrual hemorrhage occurs after the corpus luteum ceases to function. Persistence of a corpus luteum may result in amenorrhea without pregnancy. The impregnated reimplanted ovum acts with increasing intensity also directly on the endometrium toward the prevention of hemorrhage. During the first two months of pregnancy the functional activity of the ovum usually is not able to prevent the onset of a hemorrhage after removal of the corpus luteum. Exceptions to this rule occur occasionally. The death of the nonimpregnated ovum does not cause the degeneration of the corpus luteum. This occurs at a later date than the death of the ovum. The corpus luteum regresses after a predetermined period has elapsed if no new stimulus from an impregnated, reimplanted ovum keeps it alive. Wagner describes a case of amenorrhea in which he removed a corpus luteum cyst in a mature stage. Implantations from the lutein cell layer into mice produced a positive Allan-Doisy test in these animals. The endometrium was in the pregravid stage of hyperplasia. Persistence of a follicle or a follicular cyst may be responsible for metrorrhagia. The effect of corpus luteum preparations is due to the typical action of the corpus luteum hormone on the endometrium. In a second case of amenorrhea reported, multiple lutein cysts were found. The patient had all the signs of pregnancy. During the recovery from the operation the diagnosis of a benign adenoma of the anterior lobe of the hypophysis was made. The possibility of relations between this tumor and the lutein cysts on the basis of the observations of Zondek and Aschheim is considered.

W. C. HUEPER.

PARATHYROID TUMOR. I. SNAPPER, Nederl. Tijdschr. v. Geneesk. **73**:4758, 1929.

In a man, aged 56, who was affected with marked decalcification of the bones, associated with severe pains, particularly in the legs and knees, it was found that the disease had begun as generalized osteitis fibrosa cystica. There was a pseudo-

osteomalacic end-stage resembling that of Recklinghausen's disease. The calcium content of the blood serum was much increased, which was interpreted as an expression of an overactive parathyroid. There was a small tumor in the thyroid. A tumor in one of the parathyroids was suspected and was found at operation. After extirpation of this small tumor, a decided improvement in the patient's condition, amounting practically to a clinical recovery, was noted.

Pathologic Anatomy

PREMATURE INFANTS. NORMAN W. CLEIN, Am. J. Dis. Child. **37**:751, 1929.

Certain pathologic lesions produce a constant symptom-complex in the infant. Other pathologic lesions in the same infant apparently do not cause regular symptoms. The former lesions may be referred to as the chief cause of death, because of the fact that they consistently cause the same definite symptom. Infratentorial hemorrhage invariably causes intermittent cyanotic attacks.

Infratentorial hemorrhage occurred in 50 per cent of the cases in which necropsy was performed; otitis media, in 16.6; atelectasis, in 8.3; syphilis, in 11.11, and tuberculosis, in 5.5.

Pathologic lesions other than the chief lesion usually do not produce any characteristic clinical symptoms. These lesions include cortical hemorrhage, moderate degrees of atelectasis, patent foramen ovale and ductus arteriosus and mild infection. Atelectasis and infratentorial hemorrhage affect chiefly the most immature infants. Both conditions usually cause death within the first three days.

Acquired infections occur in older and heavier infants, usually after the first two weeks. The infants with tuberculosis and syphilis were older and heavier and died at a later age than the infants in the other groups.

The infants admitted when new-born or when 1 or 2 days of age who died shortly thereafter showed definite signs of immaturity of the tissues and organs. The usual cause of death was intracranial hemorrhage or atelectasis.

The infants admitted after the first week were heavier and older. The more immature infants had already died. These older infants were sent to the hospital because they were not doing well, chiefly on account of poor feeding formulas or infection.

AUTHOR'S SUMMARY.

LATE DEATH AS A RESULT OF CEREBRAL HEMORRHAGE AT BIRTH. JEROME GLASER, Am. J. Dis. Child. **37**:807, 1929.

The author reports a case of cerebral hemorrhage in which death occurred one month after birth. The hemorrhage evidently happened at the time of birth; the delayed symptoms and resulting death were the results of the organization of the blood clot around the medulla. The hemorrhage was limited to the base of the brain, pons, medulla and cerebellum.

HARRY E. LANDT.

CONGENITAL DUODENAL STENOSIS AND ATRESIA. ADOLPH G. DE SANCTIS and JOHN DORSEY CRAIG, Am. J. Dis. Child. **37**:818, 1929.

The condition in the case herein reported was diagnosed during life as pyloric stenosis. Laparotomy and exploration failed to reveal pyloric stenosis or any visible pathologic change which would explain the coexisting symptoms. Intramural duodenal stenosis was found on postmortem examination. Duodenal stenosis or atresia is probably more common than formerly thought. Congenital duodenal stenosis or atresia should be considered in any case of persistent vomiting of an apparently obstructive type during the first weeks of life or in any case presenting an atypical picture of the symptom-complex of pyloric stenosis.

AUTHORS' SUMMARY.

DISSEMINATED SARCOMATOSIS (MELANOBLASTOMA?) OF THE CENTRAL NERVOUS SYSTEM AND THE MENINGES. GEORGE B. HASSIN and PETER BASSOE, Arch. Neurol. & Psychiat. **21**:1087, 1929.

The outstanding complaints in the patient, aged 37, were pains in the legs, inability to walk, urinary disturbances and vomiting. The vision in the right eye was poor, the right optic disk was swollen and the right pupil reacted sluggishly to light; the tendon reflexes were absent throughout; the superficial reflexes were retained and on spinal puncture no fluid was obtained. The condition grew progressively worse; the paralysis became complete, the right eye became blind, the right pupil ceased to react to direct light and the sensibility was almost lost in both lower extremities. Yet the pain persisted. The necropsy revealed among other changes nodules in the peritoneum, lungs, pleura, endocardium and pericardium, small intestines, brain, cerebellum, in the stalk of the pituitary body and especially around the cauda equina. Here a soft, grayish-red tumor extended from the twelfth thoracic vertebra to the upper border of the sacrum; it entirely filled the bony canal and infiltrated the dura, the nerves and the filum terminale.

Microscopic studies showed that the tumor cells densely enveloped, ringlike, the cauda equina, entirely filling up the subarachnoid space, thus causing the absence of fluid on spinal puncture; the tumor masses were vascular and cellular; some cells contained melanin pigment which was also present in the adventitial spaces of the blood vessels; the majority of the tumor cells (of the dura, brain, stalk of the pituitary body) contained no pigment and appeared colorless. The spinal cord was not invaded by the tumor and showed no signs of compression or disfiguration; it exhibited areas of rarefaction, especially in the posterior columns of the lumbosacral cord and their degeneration in the upper thoracic and cervical regions. The changes were not unlike those seen in tabes dorsalis. It was not possible to determine the exact nature and place of origin of the tumor. It originated most likely in the cerebellum, from where it was carried along the perivascular spaces to the subarachnoid cerebral and spinal space. Here it involved the meninges, the spinal roots and the cauda equina. The circulating spinal fluid carried the cells of the tumor along the perineural root spaces into the general circulation and set up lesions elsewhere in the body. The presence of pigment suggested a melanotic tumor. The numerous classifications which were offered for the type of the tumor described are mentioned, and references are made to the extensive literature.

G. B. HASSIN.

THROMBO-ANGIITIS OBLITERANS (SPERMATIC VESSELS). A. LEE MCGREGOR and F. W. SIMSON, Brit. J. Surg. **26**:539, 1929.

A Russian jew, aged 28, presented yellowish-brown nodules at the upper and lower ends of the epididymis with slight generalized thickening of the cord and the epididymis. The veins were more involved than the arteries which the authors attribute to the rich venous return of this portion of the body. Microscopically, the picture is rather unique in that the changes vary from the acute to the chronic stages. The vessel coats were infiltrated by acute inflammatory cells, and the lumens were occluded by red clots which contained purulent foci, and in the vessels involved for a longer period of time there were organized masses that contained angioblasts and giant cells. In those in which the process was more advanced, distinct canalization of the intravascular substance was present. The authors do not mention the possibility of the periarteritis nodosa which must be considered in view of the acute inflammatory changes involving the arterial walls and the surrounding tissue, but, as the authors noted, the marked involvement of the veins as compared to the arteries is somewhat against that possibility.

RICHARD A. LIFVENDAHL.

CHOKED DISK. W. KYRIELEIS, Arch. f. Ophth. **121**:560, 1929.

Choked disk can occur in certain diseases of the blood, as the result of definite ocular changes as well as following increased intracranial pressure. Of the blood disorders, it occurs most frequently in chlorosis and in polycythemia. When choked disk is present, lumbar puncture shows that the pressure in the cerebrospinal fluid is from 100 to 300 mm. (of water) higher than normal. An ophthalmoscopic picture that cannot be distinguished from choked disk accompanying increased intra-ocular pressure can be present when the eyeball is greatly softened from a perforating injury, operation or ulcer, from a severe contusion of the eye or in a shrunken globe. Here the author thinks the mechanical factor exerted by the partial vacuum within the eyeball is important.

CHARLES WEISS.

FAT CONTENT OF LYMPH NODES. BARBARA JAEGER, Beitr. z. path. Anat. u. z. allg. Path. **80**:15, 1928.

In a morphologic study of the fat content of normal lymph nodes, axillary, inguinal and mesenteric lymph nodes were selected for examination. Fat was found to be present in all the groups studied in the form of fine dustlike particles, granules and larger droplets. It was present between the cells, as well as within the sinus endothelia, the reticuloendothelial cells and the lymphocytes. None was found in the germinal centers. It was present in slightly greater amount in the mesenteric nodes than in the other groups. The nodes of children and of those dead of wasting diseases contained a somewhat greater amount of fat than those of normal persons or of persons dead of acute disease. According to its staining reactions the material present was mixed fat and cholesterol esters.

UNUSUAL HEART ANOMALY. O. JAEGER, Beitr. z. path. Anat. u. z. allg. Path. **80**:29, 1928.

The author describes a heart obtained at necropsy from a girl, aged 9 months, and discusses the genesis of the anomaly in the light of the phylogenetic atavism theory propounded by Spitzer in 1923. The interventricular septum was defective. The right auriculoventricular valve was a typical mitral, the valve of the left side being a tricuspid the posterior segment of which was adherent to the posterior portion of the defective septum. The left tricuspid valved ventricle gave rise to the aorta, situated to the left and the pulmonary artery, situated to the right. The ductus arteriosus was patent. In the features noted the heart was an example of the not uncommon type of dextroversion, inversion and transposition, which has formed the strongest support for Spitzer's theory. The unusual feature of the heart described consisted in the presence of chordae tendinae which ran from the posterior segment of the tricuspid valve, which was situated in the left sided ventricle, through the defect in the septum, to be inserted in a strong papillary muscle on the posterior wall of the right sided ventricle. The author believes that this papillary muscle was developed from the anlage of the posterior portion of the interventricular septum, the posterior portion of the existing septum having arisen from new formative tissue which began its development after the original septal anlage had begun to be transformed into papillary muscle. In this feature as well as in the other anomalies present, the author believes the heart to offer strong support for the Spitzer theory.

LYMPHOGRANULOMATOSIS OF THE MAMMARY GLAND. H. KÜCKENS, Beitr. z. path. Anat. u. z. allg. Path. **80**:135, 1928.

In a girl, aged 16 years, swelling of the right breast was noticed several weeks before operation. At this early stage the lesion was thought to be a tuberculous abscess secondary to tuberculosis of a rib. Progressive involvement of the entire breast and induration led to a later diagnosis of a malignant condition. The surgically removed tissue, when submitted to microscopic examination, was found

to consist of characteristic Hodgkin's granuloma, with eosinophils, plasma cells and Dorothy Reed-Sternberg giant cells. Most of the glandular tissue had been replaced by the granulation tissue. The latter had diffusely invaded the underlying pectoral muscle and had extended to the left of the midline. No involvement of any lymph node group could be detected on later careful examination, and the author considers the case one of primary localization of lymphogranulomatosis in the mammary gland and the only case of this kind recorded in the literature. Kauffmann describes a case of axillary lymph node lymphogranulomatosis which involved the mammary gland and pectoral muscle by direct extension.

EFFECT OF CHOLESTEROL FEEDING ON THE LIVER AND SUPRARENAL GLANDS OF THE RABBIT. H. REINECK, Beitr. z. path. Anat. u. z. allg. Path. **80**:145, 1928.

Because of discordant results obtained by previous investigators, Reineck made a study of the effects of prolonged cholesterol feeding on the liver and suprarenal glands of rabbits, paying especial attention to normal variations in these organs and to factors other than cholesterol which might influence the lipoid content of the organs. The normal content of the suprarenal cortex in anisotropic substance was greater in winter than in summer. The oil in which the cholesterol is administered through its influence on the general nutrition of the animals, impurities in the cholesterol, the character of the food, the conditions under which the animals were kept, all were found to influence the amount of anisotropic material stored. Sesame and linseed oils when used as solvents for the cholesterol were found to have an adverse effect on nutrition; peanut oil, olive oil and mixtures of the two were much more satisfactory. When all the factors which might vitiate the effects of cholesterol were carefully controlled, the content of the suprarenal cortex in anisotropic material increased as the blood cholesterol increased. Like the latter, it reached a maximum limit beyond which further cholesterol administration had no effect. Anisotropic material made its appearance in the liver at a time considerably after a definite increase could be seen in the suprarenal gland. The quantity never became great; the material was present in both Kupffer cells and liver parenchyma. Cholesterol storage by the liver and suprarenal glands caused no apparent harm to the cells. When other agencies injured the cells, the quantity of cholesterol stored became greater than when such damage was excluded. The suprarenal cortex is held to be a regulatory mechanism in the metabolism of cholesterol, but its action in this respect is a limited one.

FATTY CHANGE OF MYOCARDIUM. H. REINECK, Beitr. z. path. Anat. u. z. allg. Path. **80**:186, 1928.

The literature relating to fatty change of the myocardium is reviewed, with especial reference to the question as to whether such change is ever physiologic. Microscopic study of 130 hearts of persons ranging in age from 1 month to 90 years led the author to conclude that the presence of fat within the muscle fibers of the heart is never an alimentary process, that the presence of fat is due to abnormal metabolism of the muscle fiber and that fat even when present in minimal amounts is pathologic.

PULMONARY SILICOSIS IN JAPAN. T. UCHIYAMA, Beitr. z. path. Anat. u. z. allg. Path. **80**:218, 1928.

Silicosis of the lung is a rare condition in Japan, probably because not many persons are engaged in stone cutting. The author reviews the literature of the subject, especially that dealing with the relation of silicosis and tuberculosis to each other, and reports three cases studied by him. These three cases occurred in a total of 1,500 necropsies in a ten year period. In one of the three cases the process was marked, in one it was slight and in all it was associated with

tuberculosis. The latter was more fibrotic in the lungs with the most marked grade of silicosis. The three patients were of the thymicolymphatic type, in which connective tissue proliferation appears to be greater, according to the author, than in other constitutional types. The tuberculous involvement of the lungs appeared to have been held in restraint by the silicotic process. In the case with the most marked pulmonary silicosis, small tubercle-like nodules were present in the liver and spleen. These were not tubercles, but silicotic nodules formed about spicules of the foreign material, indicating that the inhaled material may be transported by the blood stream.

ANNULAR PANCREAS. H. SMETANA, Beitr. z. path. Anat. u. z. allg. Path. **80**:239, 1928.

The author reports three cases of annular pancreas, one in a child, 1 month old, one in a man, aged 70 and one in a man, aged 74. The last patient was admitted to the hospital with symptoms of acute intestinal obstruction, which were found to be due to constriction of the duodenum by the encircling ring-shaped head of the pancreas. The 70 year old man was admitted for empyema. The annular pancreas was observed at necropsy. The head of the organ encircled the duodenum, constricting the latter to such a degree that the lumen would barely admit the tip of the finger. The duodenum above the constriction was dilated, and the mucosa was ulcerated. Clinical symptoms of intestinal obstruction were probably overlooked because of the empyema. In the child the annular pancreas had not caused narrowing of the duodenum. Careful dissection of the ducts showed in each case that the duct of the duodenal portion of the pancreas was the main duct of Wirsung and emptied at the papilla of Vater. The author reviews the previously reported twenty-four cases of annular pancreas and discusses the theories of origin of the anomaly. These included abnormal development of the ventral anlage of the pancreas, premature union of the ventral and dorsal anlage due to delayed rotation of the stomach and duodenum, and abnormal shortness of the main pancreatic duct. The anomaly need not cause narrowing of the lumen of the duodenum, as was evident in the child, 1 month old. Narrowing may develop later as the result of the failure of the part of the duodenum surrounded by the pancreas to take part in the normal peristalsis of the duodenum. Diabetes has been noted in a few cases of annular pancreas, and the pancreatic anomaly has been associated with other maldevelopments in a number of the reported cases.

ACQUIRED EPITHELIAL HETEROTOPIA OF THE GASTRO-INTESTINAL TRACT. H. HAMPERL, Beitr. z. path. Anat. u. z. allg. Path. **80**:307, 1928.

Under epithelial heterotopia of the gastro-intestinal tract, Hamperl discusses the occurrence of islands of epithelium of a kind not normal for the situation in which it is found. The forms recognized are: (1) squamous cell heterotopia, (2) ciliated cell heterotopia, (3) intestinal epithelial heterotopia of the gastric mucosa and (4) mucous cell or pseudopyloric heterotopia of the gastric mucosa. Two forms of squamous epithelial heterotopia are seen; that in which defects in cylinder cell epithelium are replaced by squamous epithelium by direct growth of the latter at a normal junction of squamous and cylinder epithelium, as at the esophagogastric junction and at the anorectal junction, and that in which islandic defects in a cylinder cell epithelium are replaced by squamous epithelium which has no connection with preexisting epithelium of the same type. The presence of ciliated epithelium in carcinomas of the stomach has been described by several observers, and the author presents an example of the presence of a local area of such epithelium in the noncarcinomatous gastric mucosa. He doubts, however, that such epithelium is true ciliated epithelium, but thinks that the ciliated appearance of the cells is not due to the presence of true cilia but to the loss of the cuticular zone of cylindric epithelium. The most frequent heterotopias are those in which islands of intestinal glands occur in the gastric mucosa, or glands

of pyloric type are found in the mucosa of the fundus of the stomach. Such changes are usually associated with chronic gastritis, but they are probably the result rather than the cause of the gastritis. True metaplasia of one type of epithelium into another is not the explanation of the acquired heterotopias seen in the gastro-intestinal tract. They are due, rather, to local loss of normal epithelium, which is replaced by indifferent regenerating epithelium. The latter has the potentiality of differentiating into epithelium normal for the situation or into epithelium which is heterotopic. Which course the differentiation will take depends on the physicochemical factors to which the regenerating epithelium is subjected.

LESIONS OF THE AORTA IN RHEUMATIC FEVER. H. CHIARI, Beitr. z. path. Anat. u. z. allg. Path. **80**:336, 1928.

The author discusses briefly the literature relating to the occurrence of granulomatous lesions, similar to Aschoff bodies, in tissues other than the myocardium. He states that lesions of the aorta and larger arteries have been described by few writers. He is apparently unfamiliar with the important recent American literature on this subject. In six of seven cases of rheumatic fever, the patients having died during acute exacerbations of the disease, he found involvement of the aorta and its larger branches. The lesions were situated in the adventitia and were of three types. Small, nodular, infiltrative lesions about the vasa vasorum consisted of lymphocytes, plasma cells, mast cells and large polygonal cells called fibroblast-like, but differing from fibroblasts in the chromatin distribution within the nucleus and in the basophilia of the cytoplasm. In somewhat larger, flatter lesions in the inner zone of the adventitia, a perivascular arrangement could not be seen. In such areas plasma cells and lymphocytes were less numerous than in the smaller lesions, but the large cells were more numerous and occurred as uninucleate or multinucleate giant cells. Still larger and more widespread lesions of the same composition were also seen in the inner zone of the adventitia. The larger lesions often contained fibrin at their centers, but no polymorphonuclear leukocytes. The author thinks that exudation, leading to fibrin deposition, is a later process than cellular infiltration and proliferation. In one case the lesions were older and had become partly hyalinized. In the case in which no aortic lesions were seen the myocardium was free from Aschoff bodies, and the author considers it possible that this may not have been a rheumatic infection. In his discussion of the nature of the vascular lesions described, Chiari mentions a similarity to periarteritis nodosa and to syphilitic mesaortitis. The former attacks the small arteries rather than the aorta, and syphilis involves the ascending aorta rather than the descending or abdominal portion, in which the rheumatic lesions had their situation. The media showed no changes; small areas of slight intimal proliferation were seen in the aorta. The author concludes that the vascular involvement described by him is characteristic of rheumatic fever and is probably due to hematogenous localization of the specific virus.

GASTRO-INTESTINAL LYMPHOGRANULOMATOSIS AND ICTERUS DUE TO LYMPHOGRANULOMATOSIS. C. CORONINI, Beitr. z. path. Anat. u. z. allg. Path. **80**:405, 1928.

The author reports in detail a study of five cases of Hodgkin's lymphogranulomatosis with chief involvement of the gastro-intestinal tract, and five cases of generalized lymphogranulomatosis associated with jaundice. Gastro-intestinal lymphogranulomatosis is classified as that involving the gastro-intestinal tract alone, that involving the tract chiefly and that which is part of a generalized process. In each group are placed cases of her own and from the literature in which the stomach alone was involved, cases with intestinal involvement alone and those in which lesions occurred in both the stomach and the intestine. Icterus in lymphogranulomatosis is obstructive and may be due to compression or obliteration of the common duct alone, to changes in both extrahepatic and intrahepatic ducts

or to changes limited to the intrahepatic ducts. The gastro-intestinal lesions consist of nodules which arise in the submucosa and form flattened masses which protrude in the lumen and which become superficially ulcerated; of smaller nodules scattered throughout the wall; and of broad areas of granulomatous tissue which invades the wall of the stomach or intestine widely and diffusely. Especial attention is given to a discussion of changes in the blood and the lymph vessels. The author describes proliferation of the endothelium of lymphatic channels and sinuses and of capillaries as the first stage in the formation of the lymphogranulomatous nodules and ascribes to such proliferated endothelium the chief rôle in the formation of the granulomatous tissue. In the arteries proliferation of adventitial cells may take part in the process. In both arteries and veins invasion from without may occur, or endothelial and subendothelial proliferation may lead to the formation of obliterating nodules. The latter are rarely penetrated by new formed capillaries. Obstruction of the extrahepatic bile ducts may be due to pressure of enlarged lymph nodes or to invasion of the wall by granulomatous tissue. Within the liver the interlobular ducts may become compressed by the involvement of the interlobular stroma.

CONCRETIONS OF SEMINAL TUBULES. T. OIYE, Beitr. z. path. Anat. u. z. allg. Path. **80**:479, 1928.

In the histologic examination of over 300 pairs of human testes, the author saw calculi within the semniferous tubules in six cases. When present the calculi were multiple, they had a maximum size of 200 microns, they gave the microchemical reactions for calcium and iron, and they were not dissolved by acids strong enough to cause swelling of the surrounding tissue. They were usually situated within the lumen of the tubule, but in a few instances had made their way into the interstitial tissue. The author ascribes their origin to desquamated epithelial cells, although coagulation of tubule contents may have played a part in their formation. They were laminated but did not give the reaction for amyloid. Although calculi are frequently seen in the epididymis, seminal vesicles and prostate, the author claims that they have not previously been reported within the testis itself.

ACUTE PEPTIC DUODENITIS. F. BÜCHNER and F. KNÖTZKE, Beitr. z. path. Anat. u. z. allg. Path. **80**:496, 1928.

The authors made a histologic study of three surgically resected specimens of duodenum, especially with the view of determining whether minute hemorrhages or infarctions play a part in the formation of the early peptic lesions seen in the duodenal mucosa. The lesions present varied from fresh superficial erosions to acute ulcers extending through the mucosa. No relationship to hemorrhage or infarction could be detected, and the authors ascribe the lesions to the direct action of the gastric juice. They believe that a previously normal mucosa may be injured by a gastric juice which is abnormal qualitatively or quantitatively or because of a failure of proper neutralization by pyloric or duodenal secretion. They consider the duodenal lesions seen by them similar to those described many years ago by Nauwerk as peptic gastritis.

AMITOSIS, PHYSIOLOGIC REGENERATION AND REJUVENATION. M. STAEMMLER, Beitr. z. path. Anat. u. z. allg. Path. **80**:512, 1928.

The discovery of karyokinesis relegated amitosis to the background as a process of importance in the life activities of the cell. In 1849, Bizzozero divided the tissues of the body into those in which mitosis occurs under normal conditions, the process leading to replacement of exhausted elements, that is, to physiologic regeneration; and into those in which mitosis did not normally occur and which therefore were not capable of physiologic regeneration. The first group contained most of the secreting glands, the second group the rest of the tissues. Pathologists in general have accepted the idea of Bizzozero and divide tissues into those in

which cellular replacement or regeneration occurs as a physiologic process, those in which regeneration does not occur under normal conditions but is possible under pathologic stimulation, and those in which even pathologic stimulation cannot cause regeneration, the ganglion cells of the central nervous system and the cardiac muscle being placed in the last group. Staemmler made a study of tissues in which physiologic replacement of cells has been held not to occur. The tissues studied included cardiac muscle, voluntary muscle, liver parenchyma, and renal tubular epithelium. The voluntary muscle studied was from the tongue, diaphragm, and psoas. In all the tissues investigated he found cells with two nuclei, and even with four nuclei, to be numerous. He describes and depicts the binucleate or multinucleate condition as resulting from amitotic nuclear division. The binucleate condition was seen more frequently in adults than in children. In some of the tissues, especially cardiac muscle, the amitotic formation of new nuclei apparently has a periodic rhythm. How the number of nuclei thus formed is again reduced could not be definitely determined; apparently all the nuclei did not take part in the formation of new cells, because division of the cell body of binucleate cells was only infrequently seen. In cardiac muscle Staemmler considers cellular division to be unessential for regeneration because the tissue is a syncytium. In voluntary muscle nuclear division may be a factor in the longitudinal growth of the muscle fiber. He looks on amitosis as a process which leads to rejuvenation of cells which delays the physiologic senescence and death of the cells, and which leads to the physiologic replacement or regeneration of cells exhausted by the performance of their normal functions. Each subdivision of his article opens with a valuable and concise review of the literature, biologic as well as pathologic, relating to the subject matter under discussion.

CHOLESTEROL FEEDING OF OMNIVORA. D. YUASA, Beitr. z. path. Anat. u. z. allg. Path. **80**:570, 1928.

In most of the experimental work the aim of which has been the study of the effects of prolonged cholesterol feeding, the rabbit, an herbivore, has been the animal of choice. The author questioned whether the results obtained, especially those relating to cholesterol arteriosclerosis in the rabbit, could be transferred to man, an omnivore, without reservation. He therefore studied the effects of prolonged cholesterol feeding on several species of omnivorous animals, namely, rats, mice, cats and one fox. The results in general were identical with those obtained by most previous observers in the case of the rabbit. The intima of the aorta is the site of predilection for deposition of anisotropic cholesterol esters. The latter are deposited also in the liver and in the cells of the reticulo-endothelial system, as in the rabbit. The author concludes that it is proper to use the results obtained in cholesterol experimentation on the rabbit in the elucidation of human pathology.

LOCAL EFFECTS OF VENOMOUS SNAKE BITE. W. BERBLINGER, Beitr. z. path. Anat. u. z. allg. Path. **80**:595, 1928.

Bites by venomous snakes being infrequent in Germany, Berblinger reports the results of the histologic study of the local skin and subcutaneous reaction about a bite due of the viper, *Vipera bereus*. The venom causes necrosis of the tissues with which it comes in contact, especially the capillaries. Hemorrhage and edema result. The predominant exudate cell is the polymorphonuclear leukocyte. The process set up by the bite is an exudative inflammatory reaction, in which the exudative phenomena are already well marked within an hour.

CONGENITAL DIAPHRAGMATIC DEFECT WITH UPWARD DYSTOPIA OF KIDNEY. H. O. KLEINE, Beitr. z. path. Anat. u. z. allg. Path. **80**:609, 1928.

The author presents an example of diaphragmatic defect in a female infant who lived twenty-four hours. The gastro-intestinal tract from stomach to sigmoid

was situated in the left pleural cavity, as was also the spleen. The defect in the diaphragm was limited to the left side. The left suprarenal and the upper pole of the left kidney extended through the defect into the pleural cavity. Pleura and peritoneum were united at the margins of the defect. The misplaced abdominal organs were not covered by parietal peritoneum, the condition therefore not being one of true hernia. The right lung was compressed and atelectatic, the heart was pushed to the right and there was scoliosis of the thoracic vertebral column to the right. Foramen ovale and ductus arteriosus were patent. The fetal mobile mesocolon had persisted, resulting in a mesenterium commune, which permitted the entire intestinal tract to enter the thoracic cavity. The dystopic kidney, however, was firmly attached to its underlying retroperitoneal tissue. The fetal kidney, in its normal ascent, reaches the diaphragm at or just before the time of closure of the pleuroperitoneal foramen. Kleine believes that a more rapid ascent of the kidney than normal prevented closure of the foramen and was the causative factor in the diaphragmatic defect. Ten previously reported cases of diaphragmatic defect with renal dystopia together with his case constitute a special group in which the renal dystopia was the cause of the defect. Persistence of the mesocolon may be the cause of the abnormal ascent of the kidney.

TISSUE CHANGES DUE TO REDUCED OXYGEN TENSION. A. ROSIN, Beitr. z. path. Anat. u. z. allg. Path. **80**:622, 1928.

In a previous communication, Rosin had described marked fatty change of the liver and myocardium as the result of a reduced oxygen supply. Such changes had been noted in guinea-pigs but not in mice. David had raised the objection that the results obtained were due to the reduced atmospheric pressure under which the animals were kept and not to reduced oxygen supply. In the present work the atmospheric pressure was maintained at normal, but the oxygen tension was reduced. The animals used were rabbits, rats and chickens. Rabbits were found to react like the guinea-pigs of the earlier experiments in the development of marked fatty change of the liver. Rats were unaffected, being in this respect like the mice of the previous work. Chickens also showed no changes. In the liver of rabbits and guinea-pigs, the fat was present in the central zone, glycogen being present in the peripheral zone of the lobules. Many of the cells of the central zone became necrotic. Splenectomy did not alter the results. High transection of the spinal cord caused no fatty change in rabbits under normal oxygen relations, but the characteristic changes occurred when such animals were subjected to lowered oxygen tension.

MULTINUCLEATED CELLS IN THE SEMINAL TUBULES. T. OIYE, Beitr. z. path. Anat. u. z. allg. Path. **80**:645, 1928.

In a study of a large series of human testes, Oiye occasionally saw multinucleated cells in the semniferous tubules. They may be derived from the Sertoli cells or from the spermatogenic cells, rarely by nuclear division without cell division, but more frequently by fusion of cells. The process is the result of degenerative changes in the cells.

MULTINUCLEATED GIANT CELLS IN THE SEMINAL TUBULES. A. F. KRAUS, Beitr. z. path. Anat. u. z. allg. Path. **80**:658, 1928.

The multinucleated giant cells sometimes seen in the semniferous tubules of the human testis are formed from the seminal cellular elements by fusion of the cells. According to the characteristics of the nuclei, Kraus recognizes three types of giant cells: those due to fusion of spermatids, of spermatogonia and of spermatocytes. They are formed as the result of injury to the seminal epithelium, the spermatid giant cells being formed after the slightest grades of abnormal conditions. The giant cells are cast off into the lumen of the tubule and disintegrate.

LEIOMYOMA OF ENDOCARDIUM WITH OCCLUSION OF PULMONARY ARTERY. H. ESCHBACH, Beitr. z. path. Anat. u. z. allg. Path. **80**:672, 1928.

A man, aged 58, had first complained of symptoms referable to the heart a year previous to his final admission to the hospital. At that time a diagnosis of aortic stenosis was made. When admitted he complained of loss of appetite, strength and weight, and of pain in the epigastrium, symptoms which led to a probable clinical diagnosis of carcinoma of the stomach. He was cyanotic, there was slight clubbing of the fingers, a systolic murmur could be heard over the entire cardiac area and the heart was enlarged on percussion. There was no evidence of tuberculosis. Ten days before death, he suddenly collapsed and complained of pain in the chest. The pulse was rapid and small. A probable diagnosis of infarction of the lung was made. At necropsy, the enlargement of the heart was found to be due chiefly to increase in the size of the right ventricle. The diameter of the root of the pulmonic artery was greater than that of the root of the aorta. Arising in the conus of the pulmonic artery about 2 cm. below the pulmonic valve was a firm, pale, tumor mass, which had grown upward, involving the segments of the valve, and had extended into the pulmonic artery. The growth extended in the branches of the left pulmonic artery into the lung, which was collapsed. Microscopically, the tumor was composed of dense, hyaline areas, and of other more cellular parts which contained smooth muscle, as determined by the van Gieson stain. The tumor did not appear invasive, its growth occurring in the lumen of the conus and of the pulmonic artery. The origin of the tumor was ascribed to the smooth muscle normally present just beneath the endocardium immediately below the pulmonic valve.

INTRAMESENTERIC MECKEL'S DIVERTICULUM SIMULATING REDUPLICATION OF THE ILEUM. L. KUGELMEIER, Beitr. z. path. Anat. u. z. allg. Path. **80**:682, 1928.

A girl, aged 5 months, who died of hemorrhage from a congenital ciliated cyst of the lung, had what appeared to be a longitudinal reduplication of the ileum. Beginning at a point 1.2 meters above the ileocecal valve was a tubular structure 50 cm. long. This was situated within the mesentery, its two-layered smooth muscle wall being in apposition with the muscle wall of the ileum. The structure ended blindly above, the blind end being somewhat dilated. No connection with the umbilicus could be detected. The microscopic structure was like that of the ileum. The author considers the structure described an unusually long Meckel's diverticulum, and believes that the small number of reported cases of longitudinal reduplication of the ileum are likewise examples of intramesenteric Meckel's diverticulum. (The abstracter has seen an exactly similar case of apparent reduplication of the ileum; this was held to be an unusually long Meckel's diverticulum.)

SPONTANEOUS BILATERAL PNEUMOTHORAX IN A CASE OF POLYCYSTIC LUNG. A. SCHMINCKE, Beitr. z. path. Anat. u. z. allg. Path. **80**:692, 1928.

A woman, aged 24, developed bilateral pleural effusion about a year before her admission to the hospital. The fluid was clear and contained no cells or tubercle bacilli. The difficulty in respiration with which she suffered was relieved by withdrawal of the fluid, but returned and was her chief complaint on admission. At this time she was found to have bilateral pneumohydrothorax. No evidence of tuberculosis could be found. The respiratory difficulty was again relieved by withdrawal of the fluid, but recurred from time to time as the fluid reaccumulated. She died after continuation of such symptoms for three fourths of a year. At necropsy, the lungs were compressed and each pleural cavity contained air and free, clear fluid. There were no adhesions and no tuberculous lesions. Beneath the pleura of each lung were numerous air-filled blebs, some of which had perforated through the covering pleura, thus giving rise to the pneumothorax.

The dilated air spaces were limited to the peripheral portions of the lungs and were in communication with the bronchial system. They were the dilated portions of the incompletely developed terminal bronchi. Accepting Bender's description of the development of the lung, Schmincke concludes that terminal embryonic bronchi in the peripheral portions of the lung, which are the last portions to complete their embryonic development, did not go on to the formation of air alveoli. The process is considered one of inhibition or Hemmung of fetal development, and Schmincke calls attention to the similarity of the condition described by him, considered the first reported case of its kind, to fetal bronchiectasis and congenital cystic lung, for which embryonic maldevelopment of the kind described offers the best explanation. Cystic dilatation of the undeveloped bronchi, in the walls of which there is little elastic tissue, follows. A case of spontaneous bilateral pneumothorax, identical with that reported by Schmincke, has been briefly described in Abt's "Pediatrics," vol. 4, chapter 65, p. 33.

MULTIPLE CORTICAL NECROSES OF THE KIDNEY IN PUERPERAL SEPSIS. H. GAREISS-DÖLLITZSTURM, Beitr. z. path. Anat. u. z. allg. Path. **80**:697, 1928.

In a woman, aged 36, who died of staphylococcic sepsis following her eighth delivery, the surface of each kidney was studded with numerous sharply defined, small, grayish, opaque areas of necrosis. These were limited to the cortex, through which they extended in the form of narrow streaks and wedges. Microscopically, the tissue elements within the areas were in a state of coagulation necrosis, and there was only slight leukocytic infiltration at the margins. The arteriae rectae and the vasa efferentia were occluded by hyaline thrombi, about which the tissue of the vessel wall was necrotic, but without leukocytic reaction. Bacteria could not be seen in the lesions. The author interprets the process as a deficient cellular protective mechanism in the presence of increased humoral bacteriolysis, the liberated endotoxins leading to necrosis and thrombosis of the vessels.

O. T. SCHULTZ.

A SYMPOSIUM ON CONGENITAL SYPHILIS. Verhandl. d. deutsch. path. Gesellsch. **23**:144, 1928.

G. Herzheimer-Wiesbaden declared that from 2 to 4 per cent of infants in large German cities have congenital syphilis. From 1910 to 1920 the frequency was constant; in 1922, there was an increase and during 1926 and 1927 there was a slight decrease. P. Schneider-Darmstadt discussed syphilitic osteochondritis as

Comparison of Incidence of Spirochetes and Lesions

	Spirochetes			Lesions		
	Stillborn, Per Cent	Dying Soon After Birth, Per Cent	Young Infants, Per Cent	Stillborn, Per Cent	Dying Soon After Birth, Per Cent	Young Infants, Per Cent
Liver	100	84	39	20	38	46
Pancreas	84	83	20	23	91	12
Lung	95	91	25	18	50	10
Spleen	96	84	33	15	38	33
Heart	83	83	29	0	8	4
Kidney	90	84	38	..	..	..

seen from the fifth month of fetal life to four months after birth. Periostitis was found to accompany osteochondritis constantly, at least in the region of the epiphysis. A comparison was made between the incidence of spirochetes demonstrated in them and pathologic changes in various organs.

L. Pick-Berlin presented a case of late congenital syphilitic osteochondritis in a girl, aged 11 years. The long bones had undergone a marked sclerotic reaction following caseogummatous lesions, and a certain degree of sclerosis was

also manifest in the ribs, phalanges and vertebrae. Wurm-Tübingen reported congenital syphilitic pulmonary lesions in a young woman. Chronic interstitial pneumonia and caseogummatous alterations were prominent but confined to the right lower lobe. The circumscribed character of the lesions led him to doubt their congenital nature. Danisch-Jena described changes in the sympathetic ganglions. The most constant of these were interstitial inflammation, retarded development of ganglion cells and the presence of spirochetes. He thinks that these changes may subsequently lead to trophic disturbances in the gastro-intestinal tract where the celiac ganglions are involved.

GEORGE RUKSTINAT.

THE ORIGIN OF THE HYPOPHYSEAL-SUBTHALAMIC SYNDROME. B. N. MOGILNITZKY, Virchows Arch. f. path. Anat. **269**:1, 1928.

In obesity, unrelated to increased nutrition, changes are frequently found in the neurohypophysis and the parts of the midbrain closely associated with it. The relation of the changes in the six organs to obesity in Frölich's symptom-complex is incidental. There are central forms of Fröhlich's syndrome without injury to the midbrain. Investigation of the metabolic changes should be directed to the stria system and higher centers. In investigating pathologic changes associated with this or that symptom-complex, attention should not be confined to any one particular part of the neuroglandular apparatus. There is a possibility that one part is injured primarily and the other parts are secondarily brought into relationship. On both experimental and morphologic grounds, the possibility is offered that the syndrome of diabetes insipidus is not related to injury of the hypophysis. In acromegaly, the subthalamic region and the remaining parts of the cerebrum are unchanged.

GYNECOMASTIA. F. A. BITNY-SCHLIACHTO, Virchows Arch. f. path. Anat. **269**:45, 1928.

The literature is reviewed, and cases are cited. Gynecomastia occurs following disturbances in the function of the testes and other sex organs such as the prostate, seminal vesicles and spermatic cord. The exact relationships, however, must be determined by experimental means.

THE CHANGES IN THE HYPOPHYSIS FROM VITAMIN B DEFICIENCY. S. A. SATWORNITZKAJA and W. S. SIMNITZKY, Virchows Arch. f. path. Anat. **269**:54, 1928.

In the hypophysis of pigeons, droplets of albuminous material appeared in the protoplasm of the basophilic cells most marked on the twenty-fifth day of disease. After twenty-five days, the vacuolization usually regresses, and transitions from the vacuolated to the normal cell types appear in the glands. At the same time, vacuoles appear in the eosinophilic cells, but these vacuoles could not be stained with any of many methods tried. The intralobular colloid becomes less in amount and may disappear almost completely; toward the end of the condition it reaccumulates but never to the extent present in the normal gland. The appearance of vacuoles in the cells indicates that there is an increased function related to the carbohydrate metabolism in this disease. The changes are more marked in the male than in the female pigeons and are greater in spring and summer than in winter. In rats the basophils of the hypophysis seem to be increased and the eosinophils diminished. Qualitative changes in the cells are much less in degree since the symptoms of vitamin B deficiency in rats take a long time in appearing; whatever changes there are in the hypophysis of rats are related to the carbohydrate metabolism. The necrobiotic changes in the cells of both pigeons and rats are not characteristic and are probably due to changes in the nutrition.

THE SEDIMENTATION RATE OF THE RED CELLS FROM DIFFERENT PARTS OF THE VASCULAR SYSTEM. RAPHAEL GAWRILOW, Virchows Arch. f. path. Anat. **269**:340, 1928.

Determination of the sedimentation rate in blood from various vessels of the body showed that the rate of blood from the veins is longer in internal than in peripheral blood. In the general diminished sedimentation rate this is particularly true. The sedimentation rate of peripheral blood is no index of that of internal blood. The rate depends on the plasma in which the cells are put. The addition of various substances such as sodium chloride and acacia usually led to diminished sedimentation rate. It is concluded that this rate is dependent on the physicochemical characteristics of the blood plasma.

ACQUIRED SYPHILIS OF THE STOMACH. FRANZ WINDHOZL, Virchows Arch. f. path. Anat. **269**:384, 1928.

The autopsy material in the Rudolph Hospital of Vienna showed no more gross anatomic gastric changes among syphilitic patients than others. A true syphilitic gastric disease occurred only twice in 386 autopsies of syphilitic patients; in both cases this occurred in the early stages of the disease. Those described as true syphilitic changes are: (*a*) a healed localized syphilitic disease of the stomach wall at the pylorus; (*b*) a diffuse contracted stomach, and (*c*) a circumscribed syphilitic sclerosis. A diffuse shrinkage of the stomach may occur not only from carcinoma but also from inflammation such as syphilis. The literature is well reviewed.

ATROPHY OF THE TESTES IN PULMONARY TUBERCULOSIS. A. SYLLA, Virchows Arch. f. path. Anat. **269**:480, 1928.

Examination of twenty-six persons who died from tuberculosis between the ages of 16 and 49 showed atrophic changes of the tubules in twenty-three cases.

TRIORCHISM. HENDZEL SCHLEIMER, Virchows Arch. f. path. Anat. **269**:496, 1928.

Seventeen cases of this condition were found in the literature to which one new case is added. An embryologic explanation is given.

THE HISTOBIOLOGY OF MYELOID LEUKEMIA AFTER ROENTGEN TREATMENT. FRANZ FREUND, Virchows Arch. f. path. Anat. **269**:501, 1928.

It is confirmed that leukemic cells may come from transformation of cells of the loose connective tissue, of vessel walls and of fat cells. Under the influence of the roentgen rays, leukemic cells may change back again into connective tissue cells, however, not into normal connective tissue cells but into the kind described in the scar following roentgen treatment. An exhaustive review of the literature is presented.

PERIARTERITIS NODOSA IN ANIMALS. K. NIEBERLE, Virchows Arch. f. path. Anat. **269**:587, 1928.

Ten cases have been reported in animals, one in a deer, five in swine, three in calves and one in a dog. The case reported occurred in a calf; the changes were identical with those in the disease in human beings.

NEUROMA-LIKE FORMATION IN A SHRUNKEN GALLBLADDER. H. HAMPERL, Virchows Arch. f. path. Anat. **269**:791, 1928.

A case is described in which an extraordinary increase in the number of nerve fibers was found in a gallbladder shrunken from years of cholecystitis and cholelithiasis. The picture resembled that of a similar condition described in the shrunken vermiform appendixes and in the base of peptic ulcer.

STANLEY P. REIMANN.

Pathologic Chemistry and Physics

STUDIES IN THE METABOLISM OF ALUMINIUM. F. P. UNDERHILL, F. I. PETERMAN, S. L. STEEL, E. G. GROSS, A. C. KRAUSE and A. SPERANDEO, Am. J. Physiol. **90**:1, 1929.

In a series of eight papers on the metabolism of aluminium, there are contained a description of the method used, which permits the quantitative estimation of small amounts of aluminium in biologic material, and a series of results of the several investigations conducted by means of this method. Much of the work was done on dogs. In them it was found that the blood even of fasting dogs contains perceptible amounts, which are increased after feeding diets without added aluminium. With aluminium added, this is promptly absorbed in small amounts after a single feeding, and this absorption continues for variable periods when the aluminium rich diet is continued; but eventually the absorption decreases, and with this there is a concomitant diminution in aluminium storage and excretion. The absorbed aluminium is present in the blood, and is stored especially in the liver, brain, kidney, spleen and thyroid. The bile constitutes the principal route of elimination, but after the intravenous injection of aluminium salts, it appears promptly in the urine and lymph as well. The increase in these fluids, however, is not sufficient to explain the total decrease in the blood, and there appears to be tissue storage. With diets rich in aluminium, it is absorbed by the lymph, and is excreted at all levels of the gastro-intestinal tract. The intestinal excretion of aluminium and of phosphorus are quite independent of each other. The aluminium content of tissues in the dog appeared to have a definite relationship to age, as it was present only in minute quantities, if at all, in the embryo, there were detectable amounts in the lungs of 5 day puppies, greater amounts in older animals, and considerable quantities in the lungs of old dogs. As regards aluminium in man, it may or may not occur in the blood; if present, the amount is small, the maximum found being 0.21 mg. per hundred cubic centimeters. The aluminium content of individual specimens varies from time to time within narrow limits. After a diet rich in aluminium, there may be a definite increase, but this at times is lacking. On diets poor in aluminium, there is never an increase, while a decrease in these circumstances is the rule. Aluminium is occasionally found in human urine in small amounts, and these tend to increase after the ingestion of aluminium-rich foods. But even with these it does not exceed 0.5 mg. in twenty-four hours. As regards the content of aluminium in human tissues, amounts found in the liver ranged from 0.17 to 1.17 mg. per hundred grams; in the kidney, from 0.13 to 0.87 mg. There appeared to be a geographical relationship here, presumably to be ascribed to environmental circumstances (food or water). There appeared to be increased storage with advancing age; the highest content in the liver was found, in one case, to be associated with fatty change in this organ. The report includes the results of analyses of a number of foods. No relationship could be established between the botanical grouping of vegetable foods and their aluminium content; the amounts found were sufficient to be significant. As regards the lethal effects of aluminium, a single lethal dose for rats consisted of from 7 to 8 Gm. of aluminium chloride per kilogram. Comparable lethal doses were found for the guinea-pig and rabbit. Symptoms of intoxication came on gradually—loss of appetite, followed by lethargy and depression. Autopsy observations consisted of general visceral congestion, degenerative changes of the liver, in rabbits accompanied by what appeared to be peripheral lobular necrosis, gastric distention, with swelling of the mucosa and minute areas of hemorrhage, and the occasional presence of shallow intestinal ulcers.

H. E. EGGERS.

PLASMA PHOSPHATASE IN OSTEITIS DEFORMANS AND IN OTHER DISEASES OF BONE. H. D. KAY, Brit. J. Exper. Path. **10**:253, 1929.

Lesions of the bone involving a large portion of the skeleton are accompanied by a rise in the amount of phosphatase in the plasma. In osteitis deformans and

osteitis fibrosa, this increase may be large, from four to twenty or more times the normal.

AUTHOR'S SUMMARY.

THE INDIRECT REACTION FOR BILIRUBIN IN OBSTRUCTIVE JAUNDICE. L. HOLLÓS, Klin. Wchnschr. **8**:1455, 1929.

A discussion of the interpretation of the direct and indirect van den Bergh reactions of the blood serum precedes a report of a patient with obstructive jaundice whose serums gave only the indirect test for bilirubin. These qualitative tests for bilirubin, therefore, are not differential as regards the origin of the jaundice.

EDWIN F. HIRSCH.

DISTURBANCES OF FAT RESORPTION IN CIRRHOSIS OF THE LIVER AND OTHER DISEASES. H. WENDT, Klin. Wchnschr. **8**:1566, 1929.

The observation of Bürger and Habs that in patients with cirrhosis of the liver four hours after peroral administration of 100 Gm. of olive oil and 5 Gm. of cholesterol there is no lipemia, which in health always occurs, is confirmed. Similar disturbances of fat resorption were noted with carcinoma, pericarditis, peritoneal tuberculosis and amyloidosis. Stasis in the portal system is the cause of this disturbance of fat absorption.

AUTHOR'S SUMMARY (in part).

THE K CONTENT OF PUS AND EXUDATES AND ITS RELATION TO INFLAMMATORY PAIN. C. HÄBLER, Klin. Wchnschr. **8**:1569, 1929.

The potassium content of pus and exudates increases with the inflammation. Serous exudates with a reaction corresponding to that of the blood serum have a potassium content not greater than that of normal serum. Serofibrinous and seropurulent exudates have as much as one and a half times the normal potassium content. Purulent exudates have as much as from 5.13 to 205 mg. per cent potassium, and in all of these exudates the potassium content parallels the severity of the inflammation and the degree of acidity. The increase in potassium is ascribed to the extensive destruction of the cells, from which potassium passes into the exudate. Further, in the origin of the pain with inflammation, potassium is an essential component. With serofibrinous and seropurulent exudates the reaction and osmotic tension of which are in the range that does not provoke pain, potassium is the only cause of inflammatory pain. With acute purulent exudates is the added factor of the high acidity, and this component is coupled with the increase in potassium in provoking pain.

AUTHOR'S SUMMARY.

THE EFFECT OF HORMONES IN THE SUGAR DISTRIBUTION AND CELL PERMEABILITY OF ANIMALS. R. SIEGEL, Klin. Wchnschr. **9**:1655, 1929.

Under physiologic conditions insulin furthers the localization of sugars and the glycogen fixation in the liver. In the muscle tissues it increases the penetrability of sugar and increases its synthesis to glycogen with a coincident oxidation of a small fraction. Epinephrine in smallest concentrations under physiologic conditions acts in the liver in the same way as insulin, namely, glycogen fixing. In the periphery of the body it is its antagonist so far as it hinders the transfer of sugar from the blood into the muscle. With glycogen depletion of the liver, epinephrine stimulates the new formation of liver glycogen by increasing the formation of lactic acid from muscle glycogen. Epinephrine has almost no effect on the oxidative destruction of carbohydrates. Only with abnormally high concentrations (shock, experiment) does epinephrine act in the opposite way; that is, breaking down glycogen into sugar through stimulating the sympathetic endings in the liver. Thyroxin in the liver is the real antagonist of insulin and ephinephrine, while in the periphery of the body thyroxin has no effects.

AUTHOR'S SUMMARY.

THE TRANSPORTATION OF CALCIUM FROM MOTHER TO CHILD AND CALCIFICATIONS IN THE PLACENTA. A. SCHÖNIG, Ztschr. f. Geburtsh. u. Gynäk. **94**:451, 1928.

Fresh placental tissue was left for twenty-four hours in a saturated solution of ammonium oxalate, to which a few drops of toluene were added, and put into an icebox. The tissue was then transferred into a solution consisting of equal parts of a 10 per cent solution of formaldehyde and saturated ammonium oxalate solution. Paraffin sections were made and examined under the polariscope. Calcium granules appear in the villi of from 3 to 6 months placentas. This calcium is transport calcium destined for the child. The morphologic observations and the chemical investigations prove that the resorption of calcium by the placenta is due to the functional activity of the chorionic epithelium. The basement membrane of the epithelium acts as a semipermeable membrane. The calcium diffuses from the stroma of the villi through the delicate fetal endothelium into the blood. Calcium incrustations of the mature placenta do not possess significance for the fetal life.

W. C. HUEPER.

Microbiology and Parasitology

BLOOD CULTURES AFTER TONSILLECTOMY. M. I. RUBIN, I. M. EPSTEIN and M. WERNER, Am. J. Dis. Child. **38**:726, 1929.

Blood cultures were taken from seventy-eight selected patients following tonsillectomy. All patients showed evidences of recent infections of the throat. Positive cultures were not obtained in any case.

AUTHORS' SUMMARY.

THE INFECTIVITY OF ISOLATED INCLUSION BODIES OF FOWL-POX. C. EUGENE WOODRUFF and ERNEST W. GOODPASTURE, Am. J. Path. **5**:1, 1929.

The inclusion body of fowl-pox is composed of hundreds of minute bodies enclosed in a fatty capsule. The hyperplastic epithelium of the lesion of fowl-pox, when subjected to tryptic digestion, liberates the intact inclusion bodies, while the epithelial cells undergo complete digestion. A single inclusion body, when washed with saline solution and inoculated into the skin of a hen, produced the typical lesion of fowl-pox, containing the characteristic inclusions. The fluid in which the inclusion body is finally suspended is innocuous. The inclusion bodies of fowl-pox are interpreted as being true virus bodies, i. e., minute colonies of the etiologic agent of the disease. The proliferation of the virus is accordingly largely, if not entirely, intracellular.

AUTHORS' SUMMARY.

A STUDY OF AMEBIASIS IN NEW YORK CITY. LOUIS F. BISHOP and LOUIS F. BISHOP, JR., Am. J. Trop. Med. **9**:297, 1929.

From this study of amebiasis occurring endemically in New York City, we were able to conclude that its frequency is probably greater than is commonly supposed. We were able to reach no conclusions as to the epidemiology of these endemic cases from our study, but we believe that a great deal more attention should be paid to the diagnosis of carriers of *Endameba histolytica*. More attention should be paid to the technic of microscopic examination of the feces in New York City than has been done in the past.

AUTHORS' SUMMARY.

BACILLUS CALMETTE-GUERIN (B. C. G.). S. A. PETROFF, ARNOLD BRANCH and WILLIAM STEENKEN, JR., Am. Rev. Tuberc. **19**: 9, 1929.

The B. C. G. organism in undissociated form is not very virulent for guinea-pigs and rabbits. Progressive tuberculosis occurs rarely, but it does occur. There is still ignorance in regard to the complete life cycle of the tubercle bacillus.

B. C. G. can probably be kept at a low level of virulence by cultivating it on glycerol-bile-potato medium, but if it is to be used as a vaccine, one must bear in mind that the human body is not to be compared with glycerol-bile-potato as a medium for its continued viability and development. It cannot be predicted what may happen if B. C. G. is implanted in the human body and if it is accidentally carried from human being to human being, or what transformations of it may occur. There are indications that the avirulent R (rough) organisms may be transformed into the more virulent S (smooth) ones by cultivation of the former on a medium containing their antiserum. From studies on more than 250 guinea-pigs and rabbits, it is believed that the use of B. C. G. in prophylactic immunization may be a dangerous procedure.

H. J. CORPER.

THE ISOLATION OF THE TUBERCLE BACILLUS FROM SPUTUM. MOTI MALKANI, Am. Rev. Tuberc. **19**:47, 1929.

Neither brilliant green, malachite green, gentian violet with basic fuchsin, with or without sodium ricinoleate, nor thymol in various concentrations, incorporated in the glycerol-egg medium, inhibits the growth of some of the contaminating micro-organisms (when planted in pure cultures) commonly present during the isolation and cultivation of the tubercle bacillus. A sediment of sputum digested with sodium hydroxide can be approximately neutralized by adding a few drops of normal hydrochloric acid. Accurate neutralization does not yield a higher percentage of growths. Hence, an indicator is not necessary. Such a procedure may decrease the incidence of contamination, but a strict bacteriologic technic is essential. Acid digestion may prevent the growth of tubercle bacilli from one sputum, while alkaline digestion prevents it from other sputums. Perhaps this can be explained in the light of recent studies on the dissociation of the tubercle bacillus. It seems that in order to get a constantly high percentage of primary isolations of tubercle bacilli from sputum, both methods of digestion and more than one medium should be employed.

H. J. CORPER.

MADUROMYCOSIS. K. L. PUESTOW, Arch. Dermat. & Syph. **20**:642, 1929.

Maduromycosis *(Aspergillus nidulans)* involving the head and forearm of a white girl, aged 19 years and a native of New York, is reported. The lesions healed under treatment.

FRANK M. COCHEMS.

STREPTOCOCCAL PUERPERAL INFECTION. JOHN W. HARRIS and J. HOWARD BROWN, Bull. Johns Hopkins Hosp. **44**:1, 1929.

Of 113 cases of streptococcal puerperal infection, 67 per cent showed streptococci of various varieties in the uterine cavity. Infection with aerobic, beta-hemolytic streptococci is almost always exogenous, while infection with gamma, nonhemolytic streptococci, in many cases, is probably endogenous. Aerobic and anaerobic streptococci were found with equal frequency. Almost one half of the aerobic streptococci were of the beta-hemolytic variety, and of these most were of the pyogenes group. Relatively few mannite-fermenting streptococci were encountered.

BACTERIAL CALORIMETRY: I. GENERAL CONSIDERATIONS. DESCRIPTION OF DIFFERENTIAL MICROCALORIMETER. STANHOPE BAYNE-JONES, J. Bact. **17**:105, 1929.

This paper describes modifications of the differential microcalorimeter of A. V. Hill which adapt it to study of the heat produced by growing bacteria. The chief changes are the addition of an inner vessel that can be filled with the required amount of culture fluid and sterilized. Other minor changes permit the insertion of the thermocouples without contaminating the mediums, mechanical stirring in

place of stirring by air bubbles, and the insertion of a tube for the introduction of the inoculum and the withdrawal of small samples. Data obtained from calibrations show that the apparatus is sufficiently sensitive and accurate to measure the production of approximately 6 gram calories per hour with an error of ± 1.88 per cent and the liberation of 23.68 Gram calories per hour with an error of ± 3.33 per cent in a vessel and fluid having a heat capacity equivalent to 125 cc. of water. The production of heat by cultures of bacteria is within these limits in most of the mediums employed, and it is estimated that the error in the measurements within this range is approximately ± 3 per cent.

AUTHOR'S SUMMARY.

BACTERIAL CALORIMETRY: II. RELATIONSHIP OF HEAT PRODUCTION TO PHASES OF GROWTH OF BACTERIA. STANHOPE BAYNE-JONES and HENRIETTA S. RHEES, J. Bact. **17**:123, 1929.

By means of simultaneous observations of the production of heat by bacteria and enumeration of the organisms in the culture, it is possible to correlate the curves of growth with the curves of liberation of heat. A combination of such observations with observations of the morphologic changes and other life-phases of bacteria yields some information as to the metabolic activities of a culture at various periods. By the use of Buchanan's formula, the rate of the production of heat by a single bacterial cell can be calculated, and the observed values agree closely with those derived by this calculation. Changes in the rate of the production of heat are related to changes in the rate of the growth of bacteria. Young bacterial cells produce more heat per cell than older ones. After about the fifth hour of growth, the production of heat reaches a low level and remains constant, suggesting the existence of a basal metabolic rate during that period.

AUTHORS' SUMMARY.

THE SUBMAXILLARY VIRUS OF GUINEA-PIGS. GORDON H. SCOTT, J. Exper. Med. **49**:229, 1929.

The development in the submaxillary glands of guinea-pigs of intranuclear inclusions traceable to submaxillary virus can be wholly suppressed by ligation of the gland ducts. Inclusions appear in far greater numbers in glands stimulated with pilocarpine than in ordinary spontaneous and induced infections.

AUTHOR'S SUMMARY.

THE REVERSION OF R TO S PNEUMOCOCCI. HOBART A. REIMANN, J. Exper. Med. **49**:237, 1929.

A study was made of the behavior of strains of pneumococci of the R form under various experimental conditions. It was found that daughter colonies frequently appeared among pneumococci of the R form and in some instances tended to replace those of the typical R form. The daughter strain produced colonies with shiny surfaces, which were morphologically indistinguishable from colonies of genuine S pneumococci, although, in characteristics, the bacteria comprising them conformed to the R variety. Both R and daughter forms that had resided for long periods of time in vivo were converted into virulent forms. Strains of R pneumococci which seemed irreversible were apparently converted into strains of S form by applying the methods of Griffith. A general consideration of the information derived during the recent experimental studies indicates that the virulent S form may dissociate into the R form in vivo, that pneumococci of the R form may occasionally be found in the sputum of patients with pneumonia and also may reside or lie dormant in vivo for a considerable period of time. It has been shown that under favorable circumstances the R form may spontaneously revert to the original S form or by special methods may even transform into an S form of another type.

AUTHOR'S SUMMARY.

PNEUMOCOCCUS AUTOLYSIS. WALTHER F. GOEBEL and OSWALD T. AVERY, J. Exper. Med. **49**:267, 1929.

Autolysis of pneumococci is accompanied by proteolysis, which results in an increase in amino and noncoagulable nitrogen. Autolysis of pneumococci is accompanied by lipolysis, during which there is a liberation of ether-soluble fatty acids. When extracts containing the active intracellular enzymes are added to heat-killed pneumococci, lysis of the cells occurs and there is an increase in the noncoagulable and amino nitrogen, comparable to the changes accompanying spontaneous autolysis. When extracts containing the active intracellular enzymes are added to emulsions of the alcohol-soluble lipoids extracted from pneumococci, an increase in the ether-soluble fatty acid occurs. Sodium desoxycholate in excess inhibits the action of pneumococcus protease; it does not inhibit the action of pneumococcus lipase. When suspensions of pneumococci are cooled to 0 C., a temperature at which the rate of the action of enzymes is greatly retarded, the organisms go into solution rapidly when sodium desoxycholate is added, but this process is not accompanied by lipolysis or proteolysis. It does not seem probable, therefore, that the "bile" solution of pneumococci is identical with the phenomenon of autolysis as ordinarily understood and measured. The relation of the action of enzymes to antigenic dissociation is discussed.

AUTHORS' SUMMARY.

A FATAL INFECTION OF CHICKS DUE TO BACILLI OF THE PARATYPHOID B GROUP. PHILIP R. EDWARDS, J. Infect. Dis. **45**:191, 1929.

An epizootic of chicks has been observed in which the mortality was approximately 25 per cent. Two organisms of the paratyphoid B group, *Bacterium aertrycke* and *Bacterium anatum*, were isolated from the chicks examined.

AUTHOR'S SUMMARY.

BACTERIA ISOLATED FROM INFECTIONS OF THE NASAL CAVITIES AND MIDDLE EAR OF RATS DEPRIVED OF VITAMIN A. R. G. TURNER, J. Infect. Dis. **45**:208, 1929.

A fatal septicemia may be produced in rabbits by organisms isolated from the suppurations of the upper respiratory tract and middle ear of albino rats suffering from lack of vitamin A. These organisms appear as gram-negative cocci by their morphology and by their fermentative powers. Apparently their poisonous effect is produced by an endotoxin and not by a toxic substance secreted by the organism. The toxicity for rabbits of gram-positive organisms *(Staphylococcus aureus)* found in the same rats compares favorably with the toxicity of known strains of *Staphylococcus aureus*. Organisms classified as Friedländer-like, except for one indol-producing strain, appear to be avirulent.

AUTHOR'S SUMMARY.

CARBOHYDRATE FERMENTATION, NITROGENOUS METABOLISM AND CATALASE PRODUCTION BY VARIANTS OF BACILLUS ANTHRACIS. W. J. NUNGESTER, J. Infect. Dis. **45**:214, 1929.

Seven colony variants of a stock strain of *Bacillus anthracis*, the two Pasteur vaccine cultures and a recently isolated strain of the anthrax bacillus were studied as to their carbohydrate fermentation, nitrogenous metabolism and catalase production. All strains produced acid from glucose, levulose, saccharose, maltose and dextrin and failed to ferment glycerol, lactose, galactose, raffinose, mannitol and inulin. Quantitative differences existed between the various strains in their proteolytic activity as evidenced by ammonia formation. These differences could not be correlated with virulence. Quantitative differences likewise existed between the various strains in their ability to decompose hydrogen peroxide. These differences could not be correlated with the virulence of the strain or with its pro-

teolytic activity. Thus while no differences were noted among the various cultures of *B. anthracis* studied with respect to their ability to ferment various carbohydrates, the limits of the ammonia and catalase production by the cultures studied were wider.

AUTHOR'S SUMMARY.

DISSOCIATION OF DIPLOCOCCUS FROM MEASLES. RUTH TUNNICLIFF, J. Infect. Dis. **45**:235, 1929.

As a result of aging strains of measles diplococci, two additional culture types have been obtained. The original colony is a small, smooth colony with a wide green zone (small S); the first variant is a large, smooth, less green colony with a narrow zone of partial hemolysis (large S); these two colonies in ascites plain agar are clear and smooth with regular edges; the second variant is a large, smooth, moist, slightly green colony with no hemolysis and is smooth, opaque and slightly granular on ascites agar (large SR). All forms are gram-positive. The original coccus is small, round or slightly elongated in pairs or chains; the first and second variants are large, round in pairs and clumps, the second variant often showing a capsule. The original small S culture does not ferment salicin; the two variants ferment salicin. The three culture types vary in their phagocytability, the original type is phagocytable, the first variant more so and the second variant generally not phagocytable. The small S type (Duval-Hibbard) now produces no substance toxic for paramecia, the large S type is slightly toxic and the large SR is very toxic for paramecia. The toxin from the large S type is partially neutralized by antimeasles-diplococcus goat serum and the serum of patients convalescing from measles; the toxin from the large SR type is neutralized by neither. By transplanting the three types twenty-one times in anaerobic blood agar cultures at 36 C., the small S type remained the same; the large S colonies were changed to SR, and the large SR to large S colonies, but small S colonies appear in neither the large S nor the large SR cultures. By transplanting the large S and the large SR cultures frequently in dextrose broth at room temperature or at 36 C., the large S could be changed to large SR and SR to large S colonies, but only after twenty-five transfers in dextrose broth at room temperature did the large S type revert to the small, smooth colony with a wide green zone (small S).

AUTHOR'S SUMMARY.

USE OF PARAMECIA FOR STUDYING TOXIC SUBSTANCES IN URINE. RUTH TUNNICLIFF, J. Infect. Dis. **45**:244, 1929.

The results of these experiments indicate that urine from patients with scarlet fever in the acute stage generally contains a toxic substance which kills paramecia and that this action is neutralized by scarlet fever antitoxin, but not by diphtheria antitoxin. A toxin substance is rarely found in the urine of patients after the administration of scarlet fever antitoxin and does not appear to be present during convalescence. A substance toxic for paramecia which could be neutralized by diphtheria antitoxin was rarely found in urine from diphtheria patients. A toxin neutralized by scarlet fever antitoxin was observed once in a diphtheria patient whose throat contained hemolytic streptococci. Urine from patients with measles showed no toxic substance which could be neutralized by scarlet fever antitoxin, anti-measles-diplococcus goat serum, normal goat serum or by serum from patients convalescing from measles.

AUTHOR'S SUMMARY.

THE NATURE OF BACTERIAL RESISTANCE TO BACTERIOPHAGE. F. M. BURNET, J. Path. & Bact. **32**:349, 1929.

Two bacteriophage resistant strains have been produced in which no change of phase (S or R) from the parent culture has occurred. These resistant variants are serologically identical with their parent strains. With resistance there is an

associated inability to adsorb the phage concerned with retention of the power to adsorb specifically phages that are still active against the strain.

AUTHOR'S SUMMARY.

ANIMAL STRAINS OF HAEMOLYTIC STREPTOCOCCI. J. SMITH, J. Path. & Bact. **32**:401, 1929.

A detailed study of the cultural characteristics of a number of strains of hemolytic streptococci isolated from cows, horses and guinea-pigs has not shown a possible method of differentiating animal from human strains. The exotoxin produced by certain strains obtained from cows and horses appears to be identical with the exotoxin obtained from human strains.

AUTHOR'S SUMMARY.

AESCULIN FERMENTATION AND HAEMOLYSIS BY ENTEROCOCCI. C. WEATHERALL and J. H. DIBLE, J. Path. & Bact. **32**:413, 1929.

The ability to split esculin in bile-containing mediums is a property of the enterococci. This property is slightly more widely distributed in the enterococcus-streptococcus group than is thermoresistance, which must therefore be regarded as a somewhat more specific criterion of enterococci. True hemolytic streptococci occur in the stools, but are not common. The enterococcus is typically a non-hemolytic organism; some strains, when freshly isolated, show pseudohemolysis under suitable circumstances.

AUTHORS' SUMMARY.

THE SIGNIFICANCE OF COCCAL ORGANISMS IN EXPERIMENTAL POLIOMYELITIS. R. W. FAIRBROTHER, J. Path. & Bact. **32**:435, 1929.

Cocci have been isolated infrequently from tissues of monkeys during the different stages of the disease, experimental poliomyelitis. Similar cocci have also been isolated from healthy animals, and from animals suffering from other conditions. Certain properties of the cocci have been considered. These cocci have been found to have no etiologic relationship to the disease. The cocci are members of the group of air micrococci and occur as air-borne contaminants, although under certain circumstances they may be found as terminal invaders, arising probably from the nasopharynx.

AUTHOR'S SUMMARY.

THE HISTOLOGY OF EXPERIMENTAL POLIOMYELITIS. E. WESTON HURST, J. Path. & Bact. **32**:457, 1929.

Poliomyelitis is an inflammatory disease of the whole nervous system with especial involvement of the anterior horn cells; there is at present no reason forthcoming for this peculiar distribution of the most severe lesions. The nerve cells are primarily affected by the virus, and their degeneration is not attributable to the accompanying interstitial inflammation. The cellular reaction is described in detail, and the rôle played by polymorphonuclear leukocytes and by the microglia emphasized; the various stages of evolution of the latter correspond to the "polyblasts," "elongated glial cells," etc., of the older authors. Meningitis is not a necessary feature of the disease and is often not marked in the early stages. The hemorrhages seen with some frequency result, at least in some cases, from slight trauma at autopsy to the greatly congested vessels.

AUTHOR'S SUMMARY.

BACTERIOLOGIC STUDIES OF THE UTERINE CAVITY OF PREGNANCY. FRIEDHELM ISBRUCH, Arch. f. Gynäk. **135**:108, 1928.

Isbruch's conclusions were based on bacteriologic studies of twenty-four women in pregnancies ranging from early to full term and six dogs at full term the young of which were delivered through abdominal incisions. Cultures were made from the amniotic waters and from sections of placenta and decidua. The author

found that the uterine cavity was sterile during pregnancy. However, he stated that after prolonged labor and after a long period of ruptured membranes, the uterine cavity did contain organisms that extended upward from the vagina. The author conceded also that organisms, pathogenic or potentially so, might be found in the uterine cavity with relatively short labor or with recently ruptured membranes. These organisms, however, did not always call forth a reaction on the part of the patient. Isbruch did not believe that there is a latent endometritis.

A. J. KOBAK.

THE INHIBITIVE AND DESTRUCTIVE ACTIONS OF THE ANILINE DYES. H. STÜDEMANN, Arch. f. Ophth. **122**:572, 1929.

This investigation follows up the prewar work of Römer, Gebb and Löhlein on the action of aniline dyes on germs which are pathogenic for the eye, used during the war in surgical procedures by E. Hoffmann. The author's object is to amplify the results already obtained by including organisms not heretofore subjected to this test. The more active only of the basic dyes were used: brilliant green, iodine green, gentian violet, Hoffmann's violet, malachite green, methylene violet, methyl green, saffron T, methylene blue (methylthionine chloride, U. S. P.), methyl violet, as well as the Greifswald mixture. In a test for the purity of the individual dyes, brilliant green, malachite green and methylene blue ranked first. The remainder contained varying amounts of dextrin, especially gentian violet, which, however, would not affect their action on the eye; in this regard the combination with zinc chloride in the case of methyl green should rather be considered. The effect of these dyes (in various concentrations) was tested on three strains each of *Bacillus typhosus, Bacillus coli* and the anthrax bacillus, and on two strains each of Koch-Weeks' bacillus and one each of *Bacillus diphtheriae* and *Bacillus pyocyaneus,* all of them in vitro; the maximum period of exposure was twenty minutes. Two strains of *Bacillus anthracis* only were tested on white mice.

Malachite green and brilliant green have the strongest effect on the growth of *B. typhosus, B. coli* and *B. pyocyaneus* strains; for the last-named they alone are effective. The Koch-Weeks strains were unaffected by any of the dyes. For *B. diphtheriae* malachite green, gentian violet, methyl violet, Greifswald mixture, brilliant green, Hoffmann violet, methylene violet, methylene blue and saffron T were effective, in the order given; for *B. anthracis* brilliant green, malachite green, gentian violet, methyl violet, Greifswald mixture, Hoffmann violet, methylene violet, saffron T, methyl green, and for streptothrix strains malachite green, Greifswald mixture, brilliant green, methylene violet, gentian violet, methyl violet and Hoffmann violet. Of aspergillus, *Aspergillus niger* was most affected and that by the Greifswald mixture, methyl violet, gentian violet, Hoffmann violet, methylene violet, malachite green, brilliant green and methyl green, in the order named; *Aspergillus fumigatus* was next, affected by methyl violet, the Greifswald mixture, gentian violet, malachine green, brilliant green, methylene violet and methyl green. *Aspergillus flavus* was destroyed by none of the dyes. After forty-eight hours every one of the dyes in even the lowest concentration used destroyed the anthrax bacillus. The results obtained from experimentation on white mice, using anthrax strains, make it seem justifiable to employ brilliant green, for example, in anthrax diseases of the lids, or, if toxic effects must be avoided, the next most effective dye for anthrax is gentian violet. Hoffmann violet and gentian violet in concentration of 1:50 were nontoxic for all animals; all the other dyes in this concentration and the undiluted Greifswald mixture were toxic.

CHARLES WEISS.

TUBERCULOUS RE-INFECTIONS OF THE LUNG. L. ASCHOFF, Klin. Wchnschr. **8**:1, 1929.

By re-infection of the lung is understood every new tuberculous infection from some extrapulmonic focus whether hematogenous or aerogenous. All isolated

reinfections start, according to their pathologic anatomy, with a stimulus productive of exudation, from which, as a rule, with marked resorption of the exudate, the scar stage (cartilagenous pleural scars, subpleural scars, intrapulmonic scars with or without caseocalcareous deposits) develops. According to the statistics of all pathologists, most of the reinfections heal. To such reinfections belong also thickenings in the pleural lymph nodes. Circumscribed indurations of the pleura and lungs, with few exceptions, are to be considered as specific tuberculous scars. All these small scars taken into account mean that the area of reinfection in the adult is as large as primary infection (90 per cent).

AUTHOR'S SUMMARY.

THE TRANSMISSION OF B. MURIS RATTI TO WHITE MICE. V. SCHILLING, Klin. Wchnschr. **8**:55, 1929.

The infection of the rats with *Bartonella* extended over a long period. Infection of the histiocyte giant cells of the bone-marrow and the production of methemoglobin within the body were demonstrated. Transmission of the infection occurred with eight of thirteen mice to a slight degree, and with all of eleven splenectomized mice to a marked degree. All mice developed the disease after splenectomy. Only the splenectomized mice died. The influence of the spleen in susceptibility was unquestionable.

AUTHOR'S SUMMARY.

THE TIME OF THE PENETRATION OF TUBERCLE BACILLI INTO THE REGIONAL LYMPH GLANDS AND BLOOD STREAM OF GUINEA-PIGS AFTER CUTANEOUS INOCULATION. H. MARTENSTEIN, Klin. Wchnschr. **8**:159, 1929.

In experimental tuberculosis of the guinea-pig (infective dose 0.01 mg.), the tubercle bacilli penetrated at once into the regional lymph glands following inoculation into scarified skin, and somewhat more slowly, that is, within from 1 to 2 hours, following intradermal inoculation. Tubercle bacilli were not demonstrated in the heart's blood.

AUTHOR'S SUMMARY.

AVIAN TUBERCULOSIS IN MAN. E. LÖWENSTEIN, Med. Klin. **24**:1782, 1928.

In man, avian tuberculosis begins as a sepsis with fever that may last a long time. Later, foci develop in the marrow, kidneys, skin and spleen. The diagnosis depends on the demonstration of the avian bacillus. Infected persons react to the avian tuberculin, while patients with mammalian tuberculosis do not.

THE YELLOW FEVER SPIROCHETE OF NOGUCHI IN HUMAN TISSUES. (AFRICAN YELLOW FEVER. W. H. HOFFMANN and F. JAHNEL, München. med. Wchnschr. **75**:2131, 1928.

In preparations of the liver, kidneys, lungs, heart and stomach, stained according to the old and the new methods of Levaditi, structures resembling *Leptospira* were not found.

AUTHORS' SUMMARY.

GLANDERS-LIKE PYEMIA IN A BREAST-FED NEW-BORN CHILD. ALFRED PLAUT, Virchows Arch. f. path. Anat. **270**:672, 1929.

A normally delivered, mature infant of a healthy primipara became sick at the end of the first week. The temperature was 104 F., with green liquid stools, swelling of the abdomen and finally vomiting. Death occurred on the eighteenth day of life. The liver and spleen were found studded with irregularly distributed, spherical, well outlined, yellowish-green foci, averaging in size between that of a rice grain and that of a pepper seed. One such focus was found in one kidney, and larger, less regular nodules in a lung; confluent foci diffusely involved the cecum and appendix; necrosing colitis was found in the colon ascendens; there

was diffuse serofibrinous peritonitis and pleuritis; the abdominal lymph nodes were partly supplanted by such foci; the lymph nodes at the porta hepatis were intact; the umbilical vessels were partly thrombosed, but otherwise were unchanged. The microscopic examination showed necroses with thick masses of bacilli at the periphery. The bacilli were gram-negative, short, straight or banana-shaped and resistant to any staining, only the poles and the periphery taking the strain well. Their dense, inextricable masses closely imitated mycelium. They filled the blood vessels. The reaction of the tissue surrounding the foci extended through a narrow zone only. The diffuse colitis was the result of confluent hematogenous foci. The foci in the lung were larger and less regular in shape; the bronchi were secondarily affected. The thymus and suprarenal glands were small. The skull and the organs of the neck were not examined.

Cultures from heart blood, exudates and spleen yielded *Bacterium coli*, nonpathogenic for guinea-pigs (fed and injected). The colon bacillus was not identical with the organism in the lesions. Incubation of a piece from liver in broth for ten hours did not lead to an increase in the number of bacilli within the tissue.

The source of the infection, the point of its entry and the character of the organism are unknown. The main seat of infection was the colon. Four photographs demonstrate the similarity with glanders.

ALFRED PLAUT.

IS THE PRODUCTION OF PATHOGENIC PROPERTIES IN SAPROPHYTIC STAPHYLOCOCCI POSSIBLE BY MEANS OF GEISSE'S METHOD? B. KEMKES, Ztschr. f. Hyg. u. Infektionskrankh. **109**:354, 1928.

Kemkes was unable to transform saprophytic staphylococci into pathogenic forms by means of Geisse's method, which consists in repeated passage of the nonpathogenic staphylococci in collodium sacs through the peritoneal cavities of rabbits.

W. OPHÜLS.

PANCREAS AND BACTERIOPHAGIC ACTION. E. KLIENEBERGER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **56**:32, 1928.

Bacteriophages are normally never present in sterile organs (pancreas of hog and thymus of calf). Bacteriophages can be regularly obtained from nonsterile organs of slaughtered animals. Bacteriophages are ubiquitous in slaughterhouses owing to contamination with intestinal contents. Bacteriophages can be demonstrated in the small intestine in 50 per cent of the hogs slaughtered. Sterile, raw, chopped pancreatic tissue added to bacteriophage-containing bouillon cultures hastens considerably the production of bacteriophages. Thymus acts in a similar manner. Blood tissue has a lessened effect. The causative mechanism is unknown; it does not depend on the specific pancreatic ferments nor on the action of bacteria cultured from nonsterile glands. The optimal method of producing bacteriophages is as follows: A dilution of nonsterile intestinal content in bouillon is seeded with a large amount of a lyso-sensitive strain after the addition of raw pancreas or thymus. After incubation at 37 C., the culture is filtered through Chamberland filters and tested for the lytic substance with the strain used.

WILLIAM C. HUEPER.

EXPERIMENTS ON THE FILTRABLE ELEMENTS OF THE TUBERCULOSIS VIRUS. F. KELLER and R. WETHMAR, Ztschr. f. Tuberk. **54**:22, 1929.

Pure broth cultures of tubercle bacilli and bacilliferous sputums were filtered through Chamberland filters L_2 and L_3. In spite of careful search, no acid-fast elements were ever detected in these filtrates; their cultures on optimal mediums remained sterile. In a number of series, 154 guinea-pigs were inoculated with not less than 10 cc. of these filtrates, either subcutaneously or intraperitoneally. Six of the 154 animals given injections yielded positive results. Three guinea-pigs developed a typical tuberculosis, two a strictly localized lesion, and con-

tained acid-fast rods in an enlarged gland, which on inoculation into two guinea-pigs produced typical tuberculosis. Five animals showed a moderately positive intracutaneous tuberculin reaction, but they showed no lesions at autopsy. Search for acid-fast elements in the lymph glands of injected animals was unsuccessful, with the exception of the six animals mentioned. It is concluded that the six positive results were caused by some few individual bacteria of decreased virulence having passed the filter, accidentally as it were. The control of the retentive power of bacterial filters by other bacterial strains (which was employed in these experiments) is unreliable. The positive results do not prove the existence of a "filtrable virus." If it existed, it should be possible to demonstrate its presence regularly or at least much more frequently.

MAX PINNER.

Immunology

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI. J. M. NEILL, W. L. FLEMING and A. L. HARRIS, Am. J. Hyg. **10**:1, 1929.

The paper presented two examples of the range of reacting specificity on the immediate skin reaction type of hypersensitiveness to the diphtheria-diphtheroid group of bacteria. Persons reactive with diphtheria bacilli were also reactive with many nontoxicogenic diphtheroids of diverse origin and of different fermentative properties. These examples showed that the reacting range of hypersensitiveness of a person can embrace a wide variety of strains of the diphtheria-diphtheroid group. It is probable that the subjects had been sensitized by one kind of bacteria and that the responses to the other strains were due to the immunologic relationship (not identity) to the sensitizing strain; i. e., that the hypersensitive reactions, while not strain-specific, were immunologically specific and dependent on similar group antigens among the different diphtheroids.

The results suggest that hypersensitive reactions may be given to the subsequent injection of diphtheria bacterial material by persons previously sensitized against certain diphtheroids; conversely that hypersensitive reactions may be given to certain diphtheroids by persons originally sensitized by diphtheria bacteria.

AUTHORS' SUMMARY.

SEASONAL VARIATION OF DIPHTHERIA ANTITOXIN CONTENT OF THE BLOOD OF ADULTS AND ADOLESCENTS. R. G. PERKINS, R. H. HEEREN, E. MEGRAIL and A. B. GROSSMAN, Am. J. Hyg. **10**:13, 1929.

A study has been made of the diphtheria antitoxin content of the blood in a group of school boys from 11 to 14 years of age and in adults.

A low content has been shown in the late winter and in the spring in the boys, whereas the adults whose occupations place them under conditions of exposure not too dissimilar present an entirely different picture.

This work confirms Fitzgerald's observations in demonstrating the existence of adults with practically no antitoxin in the blood, and shows also that there may be a certain number of adolescents with similar characteristics.

The authors believe that the investigation strengthens the probability that the fundamental factor in seasonal variation in diphtheria is a modification of the resistance of the individual at the actual portal of entry.

JOHN PHAIR.

RESPIRATORY IMMUNITY IN RABBITS. C. G. BULL and C. M. MCKEE, Am. J. Hyg. **10**:229, 1929.

Rabbits which have been immunized with pneumococcus types II, III or IV are completely resistant to intranasal infection with type I organisms and also manifest considerable resistance to intravenous infection with the same types.

AUTHORS' SUMMARY.

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI. J. M. NEILL, L. V. RICHARDSON, A. L. HARRIS, W. L. FLEMING and J. Y. SUGG, Am. J. Hyg. **10**: 551, 1929.

Hypersensitive immediate skin reactions may be given in response to two different products of diphtheria bacilli: a relatively stable (80 C.) substance contained in filtrates of either nontoxicogenic or toxicogenic strains, and a labile (60 C.) substance contained only in filtrates of toxicogenic strains. The tests on a previous group of adults were made with heated filtrate alone and hence did not reveal those reactive with the labile bacterial product. For this reason, a new group of adults was tested with unheated as well as with heated filtrate. Thirteen of the 2,150 persons, or 0.6 per cent of the group, gave significant hypersensitive immediate skin reactions to the diphtheria bacterial substances. The test group included white persons and negroes, and adult students and outpatients of the hospital dispensary.

AUTHORS' SUMMARY.

SEROLOGICAL DIFFERENTIATION OF STERIC ISOMERS (ANTIGENS CONTAINING TARTARIC ACIDS). K. LANDSTEINER and J. VAN DER SCHEER, J. Exper. Med. **50**:407, 1929.

In continuation of studies on the stereochemical specificity of serum reactions, antigens were examined containing the acyl radicals of the levotartaric dextrotartaric and mesotartaric acids. It was found that in this case also, immune serums can readily be obtained which differentiate sharply the three antigens which are identical in every other respect but possess stereoisomeric groups. Since the tartaric acids by their chemical constitution belong to the same class of substances as sugar acids the results have a bearing on the question of the specificity of natural antigens containing carbohydrates such as have been described by Avery and Heidelberger.

AUTHORS' SUMMARY.

THE ANTIBODY-FORMATION BY POLYSACCHARIDS. SHOJI NISHIMURA, J. Exper. Med. **50**:419, 1929.

It has been clearly demonstrated by complement-fixation tests that the serums of rabbits immunized with inulin, soluble starch and dextrin contain specific antibodies. All these immune serums gave a negative precipitation reaction. The kind of dextrin which has a construction very near to starch has an antigenic property, but those in a state of further decomposition do not give rise to antibodies. All the three kinds of polysaccharids have the power to produce antibodies without any vehicle. Dextrin is the only one of the three that gives rise to immune bodies more readily when pig serum is added to it. Regarded as antigens, inulin stood first and soluble starch and dextrin next in order. All three kinds of polysaccharids that were employed gave a negative protein color reaction. All of them, however, contained nitrogen. It has been proved that the large portion of the nitrogen contained in the soluble starch is derived from its protein contents. It is suggested that in the production of immune bodies by these three kinds of polysaccharids, proteins might play the part of the vehicle. This is, however, still to be determined.

AUTHOR'S SUMMARY.

THE ANTIBODY RESPONSE IN THE HUMAN BEING AFTER INJECTION WITH NORMAL HORSE SERUM. LOUIS TUFT and S. G. RAMSDELL, J. Exper. Med. **50**:431, 1929.

After the injection of normal horse serum in the human being, serum sickness occurs even more regularly than in patients treated with the various immune serums, but this is not accompanied by the production, to any notable degree, of circulating antibodies of the various types that are regularly to be demonstrated after the administration of immune serum and its resulting serum sickness. Since

normal horse serum therefore appears to be weakly antigenic, and immune serum highly antigenic for the human being, one must assume that this difference is the result of some alteration in its antigenic characteristics produced during the course of the immunization or of its preparation for use; or that the specific antibody which is responsible for the phenomenon of serum sickness has not yet been identified; or that this phenomenon is not in any way dependent on the presence of the various known antibodies to normal horse serum.

AUTHORS' SUMMARY.

ANTIBODY AND AGGLUTININ IN PNEUMOCOCCUS PNEUMONIA. F. T. LORD and G. E. NESCHE, J. Exper. Med. **50**:449, 1929.

Protective substances and agglutinins were not demonstrated in the blood of patients with pneumonia untreated with serum before the fall in the temperature by crises or lysis. Protective substances and agglutinins were frequently demonstrated in serum-treated patients during the course of the disease. Protective substances and agglutinins were usually present at the time of the temperature fall in patients untreated with serum and persisted for days or weeks thereafter. Protective substances have an important bearing on the outcome. A large proportion of those with protection recover and a large proportion without it die. Agglutinin and antibody may appear simultaneously or one may precede or be present without the other. Tests for agglutinin are unreliable as a control of dosage of specific serum.

AUTHORS' SUMMARY.

SKIN TESTS WITH FILTRATES AND VACCINES OF STAPHYLOCOCCUS AUREUS. M. L. AFREMOW and I. PILOT, J. Infect. Dis. **45**:167, 1929.

In a group of 1,062 persons without obvious staphylococcus infection, 417 (47 per cent) gave positive reactions after the intradermal injection of diluted filtrate. In a group of 56 patients suffering from acute or chronic infections with *Staphylococcus aureus*, 49 (89 per cent) reacted positively. Of 41 patients with diabetes, 21 (52 per cent) reacted positively. Intradermal tests with vaccine on 236 persons without obvious staphylococcic infection gave 117 (46 per cent) positive reactions. Patients infected with *Staphylococcus aureus* in a series of 36 cases gave 33 (89 per cent) positive reactions with vaccines. Individual immunity to *Staphylococcus aureus* as determined by skin tests may be influenced by intramuscular injections of filtrate or vaccine. Antitoxic rabbit and horse serums, and serum obtained from persons giving negative skin reactions neutralize the filtrates in certain dilutions.

AUTHORS' SUMMARY.

PREPARALYTIC POLIOMYELITIS: TREATMENT WITH CONVALESCENT SERUM. W. L. AYCOCK, E. H. LUTHER, C. F. MCKHANN, E. C. SMITH and S. D. KRAMER, J. Infect. Dis. **45**:175, 1929.

One hundred sixteen patients with preparalytic poliomyelitis were treated with the serum of persons convalescing from poliomyelitis. The outcome in these cases, as measured by case fatality rate, percentage of cases which developed no paralysis, percentage of cases which developed paralysis of the two severe grades, as well as by the average amount of paralysis per case is strikingly different from the outcome in untreated patients in the same outbreak. That this difference is not due in any great degree to the inclusion of patients with milder forms of the disease, which are ordinarily missed, among the treated patients by reason of diagnosis, is indicated by the close correspondence between the results in the state at large and in Watertown-Waltham, where there were increased opportunities for detecting milder forms of the disease and where a larger number of the patients were seen and treated. A relatively enormous number of missed cases must be assumed to have occurred in order to equalize the outcome in treated and untreated patients. A house-to-house canvass in one locality in which the disease

was prevalent failed to disclose the occurrence of any number of missed cases. All treated patients presented typical signs and symptoms of preparalytic poliomyelitis. The subsequent occurrence of some paralysis in 61.2 per cent of the treated patients indicates that we were not dealing largely with a nonparalytic form of the disease. Twenty-three per cent of the cases in which no paralysis developed were of the so-called dromedary type as compared with 26.8 per cent of the cases in which paralysis developed. As the dromedary phenomenon is peculiar to poliomyelitis, this is regarded as an additional substantiation of the diagnosis in the group of cases in which no paralysis developed. Of 143 patients observed for suspected preparalytic poliomyelitis, who were excluded, the majority subsequently were found to be suffering from other conditions. In only eight cases could the suggestion of abortive (not preparalytic) poliomyelitis be considered.

AUTHORS' SUMMARY.

PREPARATION OF MENINGOCOCCUS TOXIC SUBSTANCES NECESSARY FOR PHENOMENON OF LOCAL SKIN REACTIVITY. GREGORY SHWARTZMAN, J. Infect. Dis. **45**:232, 1929.

Work reported in this paper was done with filtrates of washings of meningococcus growth on 0.7 per cent glucose agar, from twenty to twenty-two hours old. Of 74 surviving rabbits in which attempts were made to elicit the phenomenon with the use of this filtrate, 73 (98.6 per cent) showed severe hemorrhagic necrotic reactions. The smallest amount of filtrate necessary to inject intradermally was 0.025 cc. As little as 0.1 cc. of undiluted filtrate per kilogram of body weight injected intravenously was sufficient to elicit severe local hemorrhagic necrosis. (Smaller amounts were not tested). The primary erythema produced by the injections of these filtrates was insignificant. There was a high general toxicity of these filtrates since doses even as small as 0.1 cc. per kilogram of body weight injected intravenously killed a certain percentage of rabbits.

AUTHOR'S SUMMARY.

DIAGNOSTIC VALUE OF THE "VACCINIA VARIOLA" FLOCCULATION TEST. W. L. BURGESS, JAMES CRAIGIE and W. J. TULLOCH, Medical Research Council, Special Report Series No. 143, 1929.

From the examination of ninety-six specimens of crusts from ninety-three cases of smallpox, chickenpox, vaccinia and other conditions, it is seen that the vaccinia flocculation test gives specific reactions of diagnostic value. The fact that the material on which these tests were carried out has been derived from different outbreaks of chickenpox and smallpox, separated in both point of time and geographical distribution, and, in the case of vaccinia, obtained from different animal species, renders it improbable indeed that the flocculation was due to interaction of adventitious antibodies in the antiserum with secondarily invading organisms or their products in the test antigens. Experiments in which vaccinia flocculating serum was absorbed with staphylococci obtained from vaccinia crusts, and subsequently tested by extracts of the same crusts, also indicate that the reaction is not due to the presence of secondarily invading micro-organisms.

The discussion of the mechanism of the reaction permits of but two hypotheses being advanced to explain its occurrence: (*a*) that a union of antigen (vaccinia or variola) with true antibodies to the virus is formed and that the floccules which appear are due to the union [the floccules may be rendered more easily demonstrable by entanglement of epithelial débris to which the virus adheres] and (*b*) that the reaction may be due to the development of heterophil qualities in the epithelium of different animal species infected with the same virus, and may therefore, to some extent, resemble the Wassermann reaction.

Without committing ourselves to an expression of opinion as to which of these two possibilities offers the true explanation of the facts observed, it appears to

us that for the time being it would be well to accept the first as a working hypothesis.

AUTHORS' SUMMARY.

THE IMMUNIZING DOSE OF VACCINIA. PETER A. CLEARKIN, Brit. J. Exper. Path. **10**:237, 1929.

Very small quantities of vaccinia virus protect against enormous doses. Before standardization of vaccine lymph becomes feasible it must be prepared in a more stable form.

AUTHOR'S SUMMARY.

THE ACTION OF AMMONIA ON COMPLEMENT. J. GORDON and P. G. MARSHALL, Brit. J. Exper. Path. **10**:249, 1929.

From the results obtained, it would appear that inactivation of complement by ammonia, i. e., destruction of the fourth component, was not associated with any interference with the protein constituents of serum or with any interference with the phosphorus partition.

AUTHORS' SUMMARY.

THE PASSAGE OF ANTIBODIES INTO THE INTRA-OCULAR FLUIDS AND THE CEREBROSPINAL FLUID AND THE EFFECT OF THEOPHYLLINE UPON IT. A. FRANCESCHETTI and C. HALLAUER, Arch. f. Augenh. **100-101**:59, 1929.

The breaking down of the aqueous humour barrier by means of theophylline in actively immunized rabbits also leads to an increased transition of agglutinins into the aqueous humour.

The agglutinin titer of the fluids of the anterior chamber is greatly increased after the administration of theophylline. Similarly, after passive immunization, the passage of agglutinins into the aqueous humour is increased by theophylline.

The permeability of the aqueous humour for hemolytic amboceptors is increased by the administration of diuretics, the actual increase being the same as for agglutinins.

Although it is scarcely possible to demonstrate precipitins in the normal aqueous humour of immunized rabbits, a constant distinct precipitate appears after the use of theophylline, particularly if double the amount of aqueous humour is used in the test.

Hemolytic amboceptors, which in normal conditions are rarely found in the vitreous humour, are present in increased quantities after injection of theophylline.

An increased passage of immune bodies into the cerebrospinal fluid could not be demonstrated as the result of the use of theophylline.

CHARLES WEISS.

THE INFLUENCE OF ANTIRABIES INOCULATION ON THE DEVELOPMENT OF THE NEGRI BODIES. F. GERLACH and F. SCHWEINBURG, Centralbl. f. Bakteriol. **110**:159, 1929.

The investigations of the authors led them to conclude that Negri bodies or the Babes-Koch-Risling granulations are not degeneration products, but are really structures of a parasitic nature. In cases of rabies negative to Negri bodies they could regularly demonstrate the latter granules, and they believe that these probably develop into the Negri bodies.

PAUL R. CANNON.

UNDULANT FEVER IN THE PROVINCE OF BRANDENBURG. W. SILBERSTEIN, Deutsche med. Wchnschr. **55**:1306, 1929.

Agglutination reactions for *B. abortus* carried out on 469 samples of blood received in the laboratory for typhoid or paratyphoid agglutination tests disclosed nine serums which gave strongly positive reactions with *B. abortus*.

PAUL J. BRESLICH.

ENCEPHALITIS AFTER SMALLPOX VACCINATION. H. G. HUBER, Deutsche med. Wchnschr. **55**:1370, 1929.

Three instances of disease of the central nervous system following vaccination against smallpox are described. In one instance in which symptoms were first noted on the fifth day after vaccination, the spinal fluid was found to contain vaccine virus by corneal inoculation into rabbits. In the other patients in whom symptoms did not appear until the twentieth day, no virus was demonstrated in the spinal fluid.

PAUL J. BRESLICH.

SENSITIZATION FROM REPEATED TRANSFUSION OF PATERNAL BLOOD OF THE SAME GROUP. P. GYÖRGY and E. WITEBSKY, München. med. Wchnschr. **76**:195, 1929.

On account of acute anemia a child of group O, 8 years old, was given several transfusions of citrated blood, the father, also of group O, serving as one of the donors. During a transfusion with the paternal blood, a typical anaphylactic shock developed from which recovery took place. The other transfusions with blood of group O, including blood from the mother, did not give rise to any unpleasant symptoms. No agglutinins or precipitins for the blood of the father could be demonstrated in the blood of the child, but mixtures of the serum of the father and the child gave complement fixation. Mixture of the serum of the mother and the child did not give complement fixation. It is also noteworthy that the intradermal injection in the child of 0.1 ccm. of the serum of the father gave a definite reaction. Such reactions were not obtained with the blood of the mother or of the child itself.

IMMUNIZATION OF CATTLE AND SHEEP BY MEANS OF B.C.G. B. LANGE and R. WETHMAR, Ztschr. f. Hyg. u. Infectionskrankh. **110**:465, 1929.

The authors state that in their experimental animals the oral and subcutaneous administration of large doses of B.C.G. was never followed by progressive tuberculosis. The subcutaneous introduction caused a stronger and more lasting hypersensitiveness to tuberculin than the feeding of large amounts of bacilli. The specific hypersensitiveness is not necessarily associated with an increased resistance to infection. After oral administration the animals were not sufficiently protected even against intravenous inoculation with a very weak virus. The subcutaneous treatment also was insufficient in part of the animals in spite of a relatively weak test infection. In the majority of the animals the treatment was successful to some extent. Two of three calves and four of six sheep overcame the intravenous mild infection which for control animals was surely fatal. These animals, however, were not free from tuberculosis. When they were slaughtered in good general condition several months later they all had limited but still active lesions. When a more virulent intravenous test infection was used, the animals did not show any specific protection. It is evident that in cattle and sheep the protection possible by means of B.C.G. is limited; in fact, the authors show that it is appreciably less than after intravenous injection of human tubercle bacilli.

W. OPHÜLS.

Tumors

INTRACRANIAL CHORDOBLASTOMA. PERCIVAL BAILEY and DUMITRI BAGDASAR, Am. J. Path. **5**:439, 1929.

These tumors are almost invariably described as having a grossly nodular but smooth surface of a milky-white color. The cut surface is semitranslucent, resembling that of cartilage, but is softer, often jelly-like. There are cysts filled with a slimy material resembling mucus. Other tumors are described as

reddish or brownish, probably owing to interstitial hemorrhage, although they are usually poorly vascularized and bleed only slightly when incised. These growths arise in the base of the sphenoidal bone and may project either upward into the intracranial cavity from the clivus blumenbachii or downward into the nasopharynx through the craniopharyngeal foramen. In several cases there was both an intracranial and an intrapharyngeal extension. There are a few cases recorded in which the tumor seems to have been confined to the nasopharynx, but in two of these there is no record of a neurologic examination and in no instance has the absence of intracranial extension been proved by necropsy. The tumor may extend into the sphenoidal sinuses, the orbits of the eyes or even into the neck and regional veins. The microscopic appearance of these tumors is remarkably uniform. The most characteristic feature is of course, the vacuolated or physaliform cells. It has been abundantly proved that the vecuoles are filled with glycogen. Since its demonstration demands fixation of the tissue in absolute alcohol, we were unable to find it in our material. But we were able to show the presence of intercellular mucin, abundant in case 1, less so in case 2. Sometimes the cells are widely separated by the mucin, causing a superficial resemblance to a chondroma; in others, they are so closely packed that the tumor resembles a small-celled carcinoma. The cells are usually arranged in groups or cords. The nature of the nuclear vacuolization, which was frequently seen in the tumor in our case 2, is still disputed. These vacuoles are said also to contain glycogen.

AUTHORS' COMMENT.

TISSUE CULTURE STUDIES OF THE GLIOBLASTOMA MULTIFORME. R. C. BUCKLEY, Am. J. Path. **5**:467, 1929.

Tissue culture preparations of ten intracranial gliomas removed at operation were made. The clinical histories and the gross structures of these tumors as seen at operation resembled previously verified examples of glioblastoma multiforme. The cultures of five of these tumors showed excellent and uniformly similar growths. The cultures of the other five tumors presented none or very little growth. The histologic structure seen in the paraffin sections of the tumor tissue from which a growth was obtained was interpreted as similar to that of the glioblastoma multiforme. A different structure in the other five tumors made the diagnosis difficult. They were interpreted as a rapidly growing glioma with cells differentiating into astrocytes. There was noted a striking similarity in the resemblance of the growing cells to those seen in fresh smears and stained paraffin sections of the same tumor tissue.

AUTHOR'S SUMMARY.

THE OCCURRENCE OF MITOSES IN NORMAL AND MALIGNANT TISSUES IN VITRO. ALBERT FISCHER and RAYMOND C. PARKER, Brit. J. Exper. Path. **10**:312, 1929.

The percentage of cells in mitosis was determined for fixed cultures of normal (fibroblasts) and malignant (carcinoma) tissue which had been cut in serial sections. The percentage of cells in mitosis in malignant tissue was found to exceed greatly the corresponding percentage in normal tissue, in spite of the fact that the growth-rate of normal tissue may exceed that of malignant tissue by 700 per cent. In cultures of normal tissue, the greatest number of dividing cells are to be found in the marginal areas. In cultures of malignant tissue, there is no appreciable difference between the number of dividing cells to be found in central and marginal regions. The degenerative phenomena occurring in cultures of malignant tissue have been described and suggestions made as to their significance.

AUTHORS' SUMMARY.

ON EXPERIMENTAL CARCINOGENESIS: THE LOCAL RESISTANCE OF THE SKIN TO THE DEVELOPMENT OF MALIGNANCY. W. CRAMER, Brit. J. Exper. Path. **10**:335, 1929.

Experiments are reported which show that when large areas of the skin of mice are subjected to chronic irritation by tar painting, the development of malignancy is confined to a small portion of that area. Any benign growths present tend to remain such, as long as the malignant tumor persists. On removing the malignant growth, however, any one of the benign growths may become malignant or an entirely new malignant process may develop in the remainder of the painted area. Removal of the second malignant growth has sometimes been followed by the appearance of a third malignant tumor. In fourteen mice in which cautery was applied to the base of a papilloma malignant changes were noted in six animals within five weeks. It is believed that these observations taken together suggest that the development of carcinoma is not dependent on changes in the epithelial cells alone but also on local inhibitory factors in the other tissues.

J. N. PATTERSON.

PROCESSES OF DEHYDROGENATION IN NORMAL AND NEOPLASTIC TISSUES. LUIGI BARELLI, Tumori **15**:533, 1929.

The author's study of the phenomena of dehydrogenation by means of meta-dinitrobenzene shows a less regular behavior with rat carcinoma tissue than with normal tissue. While Pentimalli demonstrated that blood serum exerts an activating action on dehydrogenation of tissues, the author has shown that a similar effect is exhibited by cerebrospinal fluid, milk, amniotic fluid, transudates, serum (fresh as well as boiled!) and even distilled water, but that this action is marked with normal tissues, and inconstant or absent with the adenocarcinoma of the rat.

W. OPHÜLS.

ON THE TRANSMISSION OF NEOPLASMS BY ORGANS OF ANIMALS WITH IMPLANTATION TUMORS. T. ANARDI, Tumori **15**:561, 1929.

In conformity with previous investigators, the author finds that by subcutaneous inoculation of pulp of various apparently intact organs of animals with implantation tumors, tumor formation can be produced in healthy animals of the same species. In his experiments he used rats inoculated with the adenocarcinoma type Ehrlich. Subcutaneous injection of heart blood and the inoculation of pulp of various organs of these animals caused the production of tumors in different percentages as follows: lung, 33 per cent; liver, 26 per cent; testicle, 13 per cent; spleen, 7 per cent, and blood, 4 per cent. The tumors were all of the same structure as the implanted ones. When the cellular elements in the injected materials were destroyed by mechanical, chemical, physical or biologic means which might have left a cancer producing virus intact, the results were always negative. The author concludes that the development of the tumors must be ascribed to tumor cells which were present in the circulation and in the organs of the animals with implanted tumors.

W. OPHÜLS.

CARCINOMA OF LUNG OF TIGER DUE TO PARAGONIMUS WESTERMANII. P. COHRS, Beitr. z. path. Anat. u. z. allg. Path. **81**:101, 1928.

Cohrs briefly reviews the literature relating to the occurrence of the lung fluke, *Paragonimus westermanii*, in the tiger, in the lung of which the parasite was first discovered in 1878, in the dog, cat, hog and man. He reports a case of squamous cell epithelioma of the lung in a tiger caused by the parasite. The primary tumor measured 4 by 4.8 cm. on its cut surface. Near it was a smaller metastatic nodule, and metastases were present in the bronchial and periportal lymph nodes and in the spleen. In the smaller bronchi were numerous cystic dilata-

tions caused by the parasite. In these, metaplasia of cylindric to squamous epithelium was evident; growth of the latter into the surrounding stroma could be seen. The animal had been in captivity for sixteen years. The author believes that the infestation occurred before this time and that it led to chronic inflammatory changes in the smaller bronchi, with metaplasia of the epithelium, the latter finally taking on malignant characteristics. In the duodenum of the animal were inflammatory nodules which contained the hookworm, *Galoncus perniciosus*.

O. T. SCHULTZ.

THE RELATION BETWEEN NORMAL AND MALIGNANT TISSUES. A. FISCHER, H. LASER and H. MEYER, Ztschr. f. Krebsforsch. **29**:270, 1929.

A study of the relationships between cancerous and normal tissues in vitro showed that the latter had a distinctly stimulating effect on the former, lasting as long as three weeks. The intensity of this stimulation gradually lessened. It could be separated into two phases: the first shown before the two tissues were in actual contact and due to the presence of diffusible substances, the second after direct contact was established, and due to the direct passage of material from cell to cell. On normal tissues the first effect was stimulation to connective tissue overgrowth, followed by degeneration and death. The character of the normal tissue, and even its source, was a matter of indifference, since homologous and heterologous tissues behaved alike. Of greater importance was the state of the normal tissue, the least effect being shown by those that were already killed at the time of the addition. Fresh and degenerating tissues behaved almost alike, but in any case fresh tissues degenerated rapidly. Eventually the normal tissues were completely killed and utilized by the growing tumor cells.

H. E. EGGERS.

THE HISTOLOGIC SIGNIFICANCE OF UTERINE MUCOUS POLYPI. O. HINTZE, Zentralbl. f. Gynäk. **52**:2439, 1928.

Examination was made of 225 polypi of the cervix and 57 of the body of the uterus. In seven cases of benign cervical polypi recurrences were observed. Benign cervical polypi and cervical cancer occur rarely at the same time. Still less frequent is the coincidence of malignant polypi with cancer (one case). The histologic changes present in highly epidermoid polypi may be mistaken for cancer, especially if squamous epithelial cells have advanced deeply into the glands and have replaced the cylindric lining. Serial sections are sometimes needed to trace the origin of these deeply seated squamous epithelial nests from the surface epithelium. A positive mucin stain in these nests gives evidence of their genesis. Moreover, the normal shape of the glands is well preserved. In doubtful cases, the immature character of the cells, their atypical forms, point to a malignant nature. Polypi were found in all age periods (22 to 72). The fifty-seven polypi of the body of the uterus represent 20 per cent of the total number seen in a three year period. There are two types of polypi, the myomatous and the mucous. The marked proliferation of glands, their closely packed arrangement, their irregular branching and the stratification of their epithelial lining are often suggestive of malignancy and should be considered as that, if seen in the endometrium, but have to be regarded as benign changes if restricted to the polypi, on account of the favorable clinical experiences in these cases. Seventeen cases of this type were seen in a twenty year period, and in none of them was malignancy observed later. These polypi were usually located at the fundus, only one being located in a tubal corner.

W. C. HUEPER.

Medicolegal Pathology

SUDDEN DEATH FROM HEART DISEASE WHILE MOTORING. E. R. LE COUNT and GEO. J. RUKSTINAT, J. A. M. A. **92**:1347, 1929.

Three cases illustrating sudden death from coronary and myocardial disease while motoring are reported.

ACUTE PHOSPHORUS POISONING FROM ROACH PASTE. STAFFORD MCLEAN, AILDRED MACDONALD and RUTH C. SULLIVAN, J. A. M. A. **93**:1789, 1929.

Roach paste containing 1.19 per cent elementary phosphorus is dispensed in a container which is not labeled in a manner emphasizing the danger to children from its careless use.

A portion of this paste was placed in easy access of a child, aged 18 months. Fatal phosphorus poisoning followed. This was proved chemically and by autopsy.

Chemically there was manifested liver injury as shown by a breakdown in carbohydrate, nitrogen, bile pigment, fibrin and cholesterol metabolism.

The autopsy observations indicating the harm due to phosphorus were chiefly manifested as hemorrhages in the pleura and pericardium and as lesions of the stomach, kidney, liver and striated muscle.

AUTHORS' SUMMARY.

FATAL OCCLUSION OF LARYNX BY ASCARIS LUMBRICOIDES. M. B. D. DIXEY, Edinburgh M. J. **36**:111, 1929.

Sudden death took place in a girl, aged 8½ years, from occlusion of the larynx by two large ascarid worms.

MEDICOLEGAL SIGNIFICANCE OF BLOOD GROUPS. F. SCHIFF, Lancet **2**:921, 1929.

Certain erroneous statements about the significance of the blood group in questions of paternity are discussed and corrected. More than 5,000 medicolegal examinations for blood groups have been made in Germany and the validity of the blood group test is now firmly established in this and other countries (Denmark, Sweden, Norway, Austria). Recently a committee composed of representatives of forensic medicine, serology and genetics, convened by the Reichsgesundheitsamt, expressed the opinion that the determination of the blood groups when done by an expert "is a reliable method which may be used advantageously for forensic purposes, especially for the exclusion of paternity." In about 5,500 cases, paternity was excluded in 8 per cent according to Schiff. In Germany an effort is made to safeguard officially the reliability of blood group tests.

INFANTICIDE BY THE MOTHER DURING BIRTH. G. SCHMIDT, Arch. f. Kriminol. **83**:260, 1928.

There are records of a projecting arm or even the head being severed by the mother with sharp instruments before the child has completely passed out of the birth passage, also of infanticide by stabbing the presenting intravaginal portions of the infant. The child has also been strangled when only the head was born. This report by Schmidt is another of these rare intrapartum murders. The mother beat the child's head with her bare fists so that the top and right side of the cranium was extensively fractured, and the child died a few hours after birth. When the physician arrived, the feet were still in the vagina, and the bed was bloody where the child's head lay.

E. R. LE COUNT.

AN EFFORT TO USE QUICKSILVER AS A POISON. H. KOCKEL, Arch. f. Kriminol. **83**:308, 1928.

It is not generally known that metallic mercury is relatively innocuous when swallowed. After shaking the feces of two bowel movements of an illegitimate child with a concentrated solution of potassium chloride, the feces floated and mercury noted by the mother-in-law sank to the bottom. Altogether 3,477 Gm., about 4¾ pounds avoirdupois weight, was recovered. The father had endeavored to poison the child. There were no symptoms of poisoning.

E. R. LE COUNT.

DEATH AFTER TRIBROMETHANOL ANESTHESIA. D. KALLMANN, Deutsche med. Wchnschr. **55**:1221, 1929.

A girl, aged 19, who was given 4.5 Gm. of tribromethanol in 200 cc. of water by rectum to induce surgical anesthesia, never regained consciousness and died of cardiac failure in seventeen and a half hours. At postmortem examination, there was found only an extensive superficial erosion of the lining of the large bowel, especially of the sigmoid colon. It was noted that the urinary bladder was empty although the patient had passed no urine since the anesthetic was administered. Histologically, there were marked fatty changes of the kidneys and liver.

PAUL J. BRESLICH.

THERMOMETER WOUND WITH MERCURY POISONING. DRÜGG, Deutsche med. Wchnschr. **55**:1637, 1929.

A nurse, in shaking down the column of mercury in a thermometer, injured her left index finger with broken glass. The wound healed rapidly but a swelling of the finger developed, and the x-ray examination disclosed finely divided mercury in the tissues. Symptoms of mercury poisoning were noted soon after, and these gradually became more severe in spite of repeated efforts to remove the mercury surgically. At the end of seven months, the finger was amputated and the patient recovered.

PAUL J. BRESLICH.

CARCINOMA AND TRAUMA. J. SEIFFERT, Deutsche Ztschr. f. Clin. **205**:145, 1927.

Many factors are said to be concerned with the causation of new growths. In reviewing injuries during the World War, tumor as a consequence of injury was not found. The alleged more rapid growth of tumors already existent and directly injured has little real foundation, with the possible exception of the highly malignant tumors which develop from moles when they are injured or infected. The article is theoretical and chiefly a review of literature.

E. R. LE COUNT.

DIMETHYLSULPHATE POISONING. H. STROTHMANN, Klin. Wchnschr. **8**:493, 1929.

Two patients with mild, and one with severe, $SO_2\langle^{CH_3}_{CH_3}$ poisoning were observed clinically. The symptoms are similar to those in exposure to severely irritating fumes. Important lesions, therefore, are produced in the respiratory passages and the eyes. Only a few reports of $SO_2\langle^{CH_3}_{CH_3}$ poisoning are recorded.

EDWIN F. HIRSCH.

IS THE INGESTION OF PULVERIZED GLASS HARMFUL? GREIFF, München. med. Wchnschr. **76**:1460, 1929.

The feeding to rats and cats of pulverized glass mixed with various foods failed to cause digestive disturbances or anatomic changes of the gastro-intestinal tissues.

EDWIN F. HIRSCH.

ATOPHAN AND ICTERUS. KETIL MOTZFELDT, Norsk Mag. f. Laegevidensk. **90**:283, 1929.

The different chinolin preparations (cinchophen, etc.) are now widely used in the treatment of rheumatic and arthritic pain. These preparations are recommended without restriction in textbooks on pharmacology as less toxic than the salicylates. A case of severe toxic jaundice is reported in a woman, aged 27, from phenyl-chinolin-carboxylic acid. The patient had taken 117 Gm. in two periods during two months. A review of the literature reveals several similar cases during the past two years, and at least twenty-five cases are known in all, in ten of which death occurred from acute yellow atrophy of the liver.

Technical

On the Use of a Method for the Isolation of Ascaris Eggs from Soil. L. A. Spindler, Am. J. Hyg. **10**:157, 1929.

The egg isolation technic was found to be of value in determining sources of infestations with *Ascaris* which were obscure due to the absence of soil pollution.

In areas in which soil pollution was occurring regularly the number of embryonated eggs in the sample was found to be much less than the number of one-celled and developing eggs. In one area, however, (Roaring Fork) where human stools were rarely found, embryonated eggs were much more numerous than one-celled and developing cells. This indicated that there had recently been a change in the soil pollution habits of the people in Roaring Fork.

It was found that the number of embryonated eggs in the isolations was surprisingly small, indicating that *Ascaris* eggs die much more rapidly in the soil than is commonly believed. This suggests that *Ascaris* eggs do not live over the winter in any number and that infestations in the spring are dependent on the development of a new crop of eggs and not on those living over from the previous fall.

Author's Summary.

Dextrose in Synthetic Mediums for the Tubercle Bacillus. R. R. Henley, Am. Rev. Tuberc. **19**:660, 1929.

Synthetic mediums containing dextrose afforded a more rapid growth of *Bacillus tuberculosis* than did the same mediums free from sugar. The results confirmed the recently reported observations of Frouin and Guillaumie, since it was found that the growth of *B. tuberculosis* on synthetic mediums was influenced by the relative proportion as well as by the actual amount of the different constituents of the mediums. A medium is described which in six weeks afforded yields of bacteria weighing 2 Gm., dry weight, per hundred cubic centimeters of culture fluid.

H. J. Corper.

Observations on Some of the Factors Involved in Filtration Experiments. Francis B. Grinnell, J. Bact. **18**:175, 1929.

Neither the rate of flow of distilled water nor the pressure required to bubble air through a filter under water is a safe guide as to whether or not the filter will hold back bacteria. An old culture of *B. prodigiosus* will pass through a filter which is impermeable to a young culture. The nature of the suspension fluid is of great importance in determining whether or not particles of a given size will pass through a filter. Victoria blue B will pass through Berkefeld filters, if dissolved in hormone broth. Young cultures of *B. prodigiosus* will pass through Berkefeld filters V and N, if suspended in a modified hormone broth or in alkaline extracts of certain animal or vegetable cells. The chemical composition of the substance present in hormone broth and in certain cell extracts which facilitates filtration through Berkefeld filters has not been determined.

Author's Summary.

A New Fixative for Mitochondria. J. Gough and J. D. Fulton, J. Path. & Bact. **32**:765, 1929.

Mercuric acetate may be used as a fixative for mitochondria after simple formaldehyde fixation. The chemical action is the formation of addition compounds with unsaturated centers. The intense staining with acid fuchsin after this fixation is accounted for by the capacity of mercuric acetate to form an insoluble purple compound.

Authors' Summary.

SPUTUM EXAMINATIONS IN TUBERCULOUS PATIENTS. E. BAJZA, Beitr. z. Klin. d. Tuberk. **72**:202, 1929.

So-called concentration of the sputum with antiformin for the bacterioscopic demonstration of tubercle bacilli is useless. In 99 per cent of all bacilli-carrying sputums, elastic fibers were demonstrated.

MAX PINNER.

A SIMPLE METHOD FOR BILATERAL THORACOGRAPHY. ANTHONY and HANSEN, Beitr. z. Klin. d. Tuberk. **72**:217, 1929.

A simple apparatus is described by which the excursions of any point of the chest wall can be accurately recorded.

MAX PINNER.

RAPID HISTOLOGIC DIAGNOSIS OF MALIGNANT TUMORS. R. DENGLER, Zentralbl. f. Gynäk. **53**:457, 1929.

A rice seed size piece of tissue removed from the suspected part is dissected with the help of two needles in 0.9 per cent NaCl solution. It is examined with high magnification and almost closed diaphragm after the addition of a drop of 1 per cent acetic acid. The nuclei of the tumor cells are counted according to their size. The smallest nuclei present are counted with 1, the nuclei twice the size with 2, etc., to 7. The result is expressed as a quotient of the number of different sizes counted divided by the total number of nuclei counted. If fifty nuclei are counted, the quotient for carcinomas is always above 0.1, usually 0.14. The range, in general, is from 0.06 to 0.14 (from 3/50 to 7/50). The diagnoses were made from fresh tissue in 100 cases and later substantiated from sections prepared with the usual methods.

W. C. HUEPER.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Nov. 14, 1929

J. HAROLD AUSTIN, *Presiding*

THE OCCURRENCE AND SPREAD OF TUBERCULOUS INFECTION. EUGENE L. OPIE.

I shall present a conception of tuberculosis by no means new which explains many obscure aspects of its pathogenesis and promises to modify profoundly procedure for its control. Briefly stated it is that tuberculosis of early life has the characters of a first infection, whereas tuberculosis of later life is a disease modified by acquired immunity.

Tuberculosis in infancy and early childhood resembles that produced experimentally in susceptible animals. Pulmonary tuberculosis in adults has, however, little resemblance to tuberculosis produced by the usual inoculation of animals. In sharp contrast with the tuberculosis of early childhood it long remains localized in the parenchyma of the lung and even though a whole lobe is implicated the lymph nodes at its hilus exhibit none of the characteristic changes of tuberculosis.

Roentgenologic films prepared from lungs removed after death are an effective aid in the discovery of the calcified scars of healed tuberculosis acquired during childhood. By this means, one seldom fails to obtain proof that those who die from the chronic pulmonary tuberculosis usual in adults have sustained an earlier infection.

Human pathology furnishes a significant illustration of the danger accompanying protective inoculation. The early tuberculous infections of childhood afford a certain degree of protection against reinfection and when it occurs profoundly modify its course, yet these childhood infections vary widely in intensity and even when long concealed or latent may ultimately cause active disease and death.

Changes that occur at the site of reinfection with tubercle bacilli resemble closely those that occur in animals sensitized to foreign protein. When foreign protein is first injected into the skin of a normal animal it rapidly leaves the site of injection and enters the circulating blood. In the animal that has been immunized (and sensitized) reinjection with the foreign protein produces an intense inflammatory reaction with necrosis at the site of entry; the foreign protein is arrested by the inflammatory reaction at the site of injection, and fails to enter the circulating blood. Krause and Willis have recently demonstrated by inoculation of excised tissue into guinea-pigs that there is in normal guinea-pigs rapid dissemination of tubercle bacilli from the site of inoculation, whereas in animals previously infected dissemination is retarded.

Experimental transmission by contact rather than by inoculation is a method of study that has not received the attention it deserves. Systematic studies of the experimental epidemiology of tuberculosis have been made by Perla and by Lurie at the Henry Phipps Institute. A large part of those who are engaged in the experimental study of tuberculosis believe that spontaneous tuberculosis of guinea-pigs occurs seldom if at all. When normal guinea-pigs were kept in cages with others that were infected, from 22 to 60 per cent acquired tuberculosis after about seven months, the number varying with crowding and other conditions.

At the present time the epidemiology of human tuberculosis can be studied more satisfactorily than that of animals.

Until the last few years little has been known concerning the distribution and severity of tuberculous infection among those who give no evidence of the disease and are presumably in good health. It is evident that no accurate knowledge

of the epidemiology of tuberculosis is obtainable as long as these latent infections are ignored. During the last six years, the dispensary of the Henry Phipps Institute has been organized to assemble by its routine operation information concerning the occurrence of latent as well as clinically manifest tuberculosis, to trace the spread of infection by contagion within the household and elsewhere and finally to determine by observations continued over a period of years under what conditions latent develops into manifest disease.

A study of the spread of tuberculosis in families has been undertaken by Dr. McPhedran and me. This study has demonstrated how frequently advanced latent lesions develop into manifest disease. The recognition of advanced latent tuberculosis furnishes a means by which the onset of tuberculosis may be predicted within certain limits years even before it has begun to undermine health. Roentgenologic studies have revealed the frequency with which apical lesions occur in adolescent children of families exposed to open tuberculosis. In families in which husband or wife suffered with open tuberculosis we found evidence that the infection had been transferred to the consort in nearly half of those who were examined.

A survey of tuberculosis among children in the public schools of Philadelphia made by Dr. Hetherington, Dr. McPhedran, Dr. Landis and me during the last three years has revealed the frequency with which infection varying in character and extent occurs in children who are presumably healthy. This survey has shown that 0.5 per cent of the school children we examined have manifest tuberculosis recognizable by physical examination and roentgenologic films. Latent tuberculous infiltration of the lungs of the type of childhood was found in 2 per cent of children and was evidently more significant in younger children. Latent apical tuberculosis (adult type) was found in 1 per cent of children, in large part in high-school pupils between the ages of 15 and 18 years. Of boys of high-school age, only 0.4 per cent had clinically recognizable tuberculosis, whereas of girls 1 per cent was affected. Manifest tuberculosis was found in 0.6 per cent of white children between 12 and 18 years of age and in 2.4 per cent of colored children of the same ages.

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Nov. 21, 1929

HARRISON S. MARTLAND, *President*

POSTMORTEM BLOOD CHEMISTRY IN RENAL DISEASES. SILIK H. POLAYES and EDITH HERSHEY (by invitation).

Chemical analyses, including that of the creatinine and urea content were made post mortem on the blood of 100 patients with various diseases. Only those cases were chosen in which previous chemical analyses were made during life, so that comparisons could be made between antemortem and postmortem determinations. It was found that the postmortem figures for urea were highest in those cases which showed high postmortem creatinine values, namely, in the cases of renal disease with average antemortem creatinine values of 5.6 mg. per hundred cubic centimeters of blood. The figures for urea, however, were found to be unreliable as an index of the antemortem renal status. The creatinine values post mortem, on the other hand, were found to be helpful in determining the status of the renal function during life. Whenever the postmortem figures for creatinine were 4 mg. or more per hundred cubic centimeters of blood, the values obtained during life were over 3 mg. per hundred cubic centimeters of blood, and there were other evidences of severe renal disease clinically as well as anatomically.

1. Postmortem determinations of blood creatinine and urea are often helpful as an aid in obtaining the status of the renal function during life.

2. The values for urea are not as helpful as those for creatinine.

3. A creatinine content of 4 or more mg. per hundred cubic centimeters of blood post mortem indicates marked retention of creatinine during life and therefore severe renal insufficiency.

CHANGES IN THE INTRAHEPATIC BILE DUCTS FOLLOWING CHOLECYSTECTOMY: AN EXPERIMENTAL STUDY. JOHN E. SUTTON, JR. (by invitation).

For a number of years, certain changes in the biliary system have been known to occur following cholecystectomy. In 1917, Judd and Mann reported the dilatation of all of the extrahepatic ducts after the removal of the gallbladder, and they showed that this is due to the action of the sphincter of Oddi. Sweet has observed a marked rise in the blood cholesterol following cholecystectomy. Normal values were not found for forty days or more after the operation. The development of jaundice after obstruction of the common duct is distinctly influenced by the loss of the gallbladder. In normal dogs, according to Mann and Bollman, bilirubinemia develops in from twenty-four to thirty-six hours following ligation of the common duct, whereas after cholecystectomy bilirubinemia develops in from three to eight hours after biliary obstruction. The parietal sacculi, which are normally found as small pouches extending from the lumen into the fibrous walls, enlarge to an appreciable degree following cholecystectomy, and it has been suggested that this enlargement compensates in a way for the loss of the gallbladder. In animals which do not possess gallbladders there is evidence of a mechanism capable of performing some functions of a gallbladder. In the horse there is an elaborate development of the parietal sacculi, according to Sweet; in the rat, as shown by Higgins, there is an extensive system of blind tubules in connection with the intrahepatic bile ducts, which twine about the branches of the portal vein. Furthermore, the liver bile of the rat, as estimated by McMaster, contains eight times as much pigment as the liver bile of the mouse, which possesses a gallbladder.

In this study, simple cholecystectomy was performed in eighteen dogs which were allowed to survive for varying periods of time up to seventy-seven days. The animals were killed with ether, the livers were removed intact and a 12 per cent solution of silver gelatin was injected through the common duct, under a pressure of from 100 to 180 mm. of mercury, until the biliary system was completely filled. Under a constant pressure the specimens were placed in an ice-cold 5 per cent solution of formaldehyde which hardened the gelatin and fixed the tissue. Six normal dogs' livers were treated in the same manner and used as controls. Microscopic sections of the gallbladder and the intrahepatic bile ducts of the normal dogs, and sections of the intrahepatic ducts of the dogs 15, 22, 40 and 77 days following cholecystectomy were studied. The original intent was to study the changes which occur in the parietal sacculi following the removal of the gallbladder, but a study of the sections revealed changes of far greater importance.

Without exception, all sections from the controls show that there was a normal cuboidal epithelium in the intrahepatic ducts, and that the mucosa of the gallbladder was covered with high columnar cells normally arranged on folds projecting into the lumen. The duct epithelium following cholecystectomy showed definite changes in all specimens. Fifteen days after operation the surface of the epithelium was irregular; new cells projected into the lumen of the ducts, and there was apparent bud formation. These projecting cells contained light staining, large, irregular nuclei and their margins were not clearly defined. In many areas the cells were present in multiple layers. Forty days after cholecystectomy, well defined alterations of the duct epithelium were seen. Numerous mucous folds and villi of varying size were seen projecting into the lumen of the ducts, and the epithelial cells were elongated and roughly oval; the cells approached the morphologic appearance of the epithelial cells of the gallbladder. The appearance of the duct epithelium seventy-seven days after cholecystectomy fulfilled the promise of the earlier changes. The mucous folds were longer and

the epithelial cells were high columnar with oval or elipsoid nuclei, the long axes of which were perpendicular to the bases of the cells. The microscopic picture of the tip of one of these mucous folds was identical with that of the tip of a mucous fold in the normal gallbladder.

The only operative procedure used in this investigation was simple cholecystectomy, which was done on eighteen dogs; no injections of any material were made into the bile ducts while the dogs were alive. The injection of the gelatin solution after death served to distend the ducts and to prevent distortion of the walls of the duct during the fixation in formaldehyde. Therefore all projections found in the lumina of the ducts were true mucous folds and were not due to infolding of the walls of the duct.

In the normal dog, removal of the gallbladder is followed by prompt changes in the intrahepatic bile duct epithelium. In this study these changes have been followed in sequence. The development of mucous folds in the ducts, increasing the epithelial surface to a marked degree, and the change of the epithelial cells from the cuboidal type, with no real resemblance to the gallbladder cells, to high columnar cells having morphologic characteristics identical with those of the normal gallbladder lead to one conclusion. Removal of the gallbladder is followed by compensatory changes in the intrahepatic bile duct epithelium; these changes must mean that the bile duct epithelium can adapt itself to perform functions of the gallbladder.

From the examination of a number of specimens of human livers (by permission of Dr. Krumbhaar, McManes Laboratory of Pathology, University of Pennsylvania) it appears that these changes also occur in human beings after cholecystectomy and in the presence of chronic cholecystitis and cholelithiasis.

SOME OBSERVATIONS ON BLOOD GROUPING. ARTHUR M. TIBER (by invitation).

Ten thousand specimens of blood were examined for grouping by the open macroscopic method of Vincent; 46.5 per cent fell into group O, 36.4 per cent into group A, 13.5 per cent into group B and 4.5 per cent into group AB. The material used for testing these specimens consisted of pooled specimens of group A and B serums. The grouping of the red cells was without fault in 9,985 specimens of blood. Fifteen showed questionable agglutination because they were either clotted or very anemic. The serum of a small number of persons was tested with known red cells and it was found that in nine cases the typing did not check with the results obtained by typing the red cells. In five cases, in which the donor and the recipient were of the same group, there was agglutination when the bloods were cross-matched. In 1,467 transfusions of blood there were but 2 deaths, one as a result of an error in technic and the other as a result of the use of a so-called universal donor; 10,242 cases of blood transfusion were collected from the literature, with 22 deaths from all causes in this series: 13 due to wrong types, 1 to primary disease, 4 to heart failure and 4 to unknown cause.

The following conclusions were given: The open macroscopic method of Vincent is efficient for determining the blood group of recipients and donors. Serum for testing should consist of pooled specimens of group A and B serums. Grouping by this method should be determined by testing the red cells alone. The classification of bloods into four groups is sufficient for the purpose of transfusion. The death rate for transfusions of blood is 0.39 per thousand.

DISCUSSION

PERRY MANHEIMS: About five years ago, at the Lenox Hill Hospital, a patient who was receiving a transfusion of 100 cc. of blood, showed symptoms of a typical transfusion reaction of incompatibility. The transfusion was stopped, and although the reaction was severe, the patient recovered. That was one case in which we did not do a cross-test because it was an emergency and we were hurried by the attending physicians. Since that time no transfusion, no matter how urgent,

has been done without a cross-grouping. We have not had any mortality. I believe that every case should be grouped and cross-tested, in addition to the grouping.

PHILIP LEVINE (by invitation): I should like to make a comment concerning the significance of the irregular reactions in general. Dr. Landsteiner and I have examined numerous serums by the use of a sensitive technic and we have found that about 3 per cent of serums showed distinct atypical reactions at 20 C. At 37 C. most of the reactions disappeared. About ten serums were observed which showed a distinct type of specificity.

The agglutinable property indicated by this agglutinin is influenced by heredity. A difference in its distribution in colored and white persons is also shown.

Another distinct type is a so-called subgroup division in group A. We found two atypical agglutinins α^1 and α^2 in some serums of groups A and AB. Group O cells, which are supposed to be characterized by lack of agglutinogens, react with agglutinin α^2.

In agreement with Dr. Tiber's paper we believe that there is not sufficient evidence at present that transfusion in cases with typical reactions is harmful.

REUBEN OTTENBERG: I do not entirely agree with Dr. Tiber for this reason. I think the minor differences that are pointed out by Guthrie and Houck probably do not lead to fatal results, but they can readily lead to errors in grouping. That is to say, there are certain persons belonging to group B whose serum will fail to agglutinate that of persons in group A; knowing that the person's cells have been grouped as group B, if one simply uses that serum as a group serum, and depends on it alone, one can readily make a mistake. The fact is well recognized. In a study of blood groupings, Guthrie and Houck were the first to emphasize that this particular subdivision occurred. If a person in group B has only serum agglutinin α and a person in group A only red cell agglutinogen α^2, one serum will fail to agglutinate the other. Only this week an intern was puzzled by such a case: A person with different sets of typing serums was put down as type B, and then as a type AB. On going over the problem with him more carefully and testing the serum of the subject we found that there was a type B in the test serums which failed to agglutinate certain serums of group A. For that reason, I feel that if one knows all about the subject, is aware of these occasional happenings, and always uses two or three serums of each type to do one grouping, then it is safe to go ahead and rely only on grouping. But if one works in a routine way one may now and then have a serious accident in the grouping itself. For that reason I think one should always, except in emergency, do cross-tests as well as grouping.

With regard to extra-agglutinins, two or three years ago I published a case in which death from hemolysis followed blood transfusions in which an irregular agglutinin was demonstrated. I do not know whether this is extra-agglutinin I of Levine or another of the irregular agglutinins. We have not been able to identify it because the donor, who was a professional donor, would not come back for further investigation. Death was undoubtedly caused by hemolysis; the recipient and the donor both belonged to group B, except for the extra-agglutinin that agglutinates and hemolyzes the cells of certain other persons in all four groups.

JACOB WERNE (by invitation): A practically important and frequently neglected factor in performing the matching is that of time. I wonder whether any of the anomalous observations reported in Dr. Tiber's series may not have been made because insufficient time was allowed for agglutination to occur. Several times in doing the routine cross-match, I have had the unpleasant experience of reporting compatibility after waiting the conventional twenty minutes, only to notice by chance some fifteen minutes later the occurrence of definite agglutination. Dr. Scannell once suggested to me that placing the preparation in the icebox would accelerate agglutination, if this were going to occur. I have found this measure of considerable help.

SILIK H. POLAYES: We ought to be a little more careful in distinguishing the reactions due to anaphylaxis from those due to interagglutination. At the Jewish Hospital in Brooklyn, we recently had a case in which the anaphylactic reaction following a transfusion so closely simulated an interagglutination reaction that it was difficult to differentiate it clinically. We sent the blood to the Rockefeller Institute. Dr. Levine analyzed it and found nothing irregular about it. Both the donor and the patient were of group A. We are now certain that it was an anaphylactic phenomenon. In a subsequent transfusion in the same case, the reaction was definitely controlled by the injection of epinephrine. I feel certain that a good many of these reactions reported as interagglutination reactions are really not such, but are simply anaphylactic reactions.

ARTHUR M. TIBER: One of the speakers suggested placing the reaction slides in the icebox. It is well known that cold agglutinins act at icebox temperature 0 C. More confusion would be found if the slides were placed in the icebox than if they were kept at room temperature. If he had said at 36 C., I would be more apt to agree with him, because many of the irregular reactions can be ruled out at that temperature.

We use the open macroscopic method of Vincent and watch the reaction for from five to ten minutes only. Any one who has used this method knows that after thirty minutes' observation he has a clot on his slide, with nothing to read.

As to Dr. Ottenberg's statement, I think it is true that the serum of certain patients is weak in iso-agglutinins, and if one uses serum from but two persons for testing purposes the results may be fallacious. At Bellevue we have avoided these errors by pooling the serums of the same type. In this way, if an anomalous serum is included, it is diluted by the other normal serums, and instead of lacking an iso-agglutinin, we have the normal titer of iso-agglutinin.

Dr. Levine's statement about the subgroups is an important one, particularly in forensic medicine. As to the necessity of determining the presence or absence of these subgroups, I think it is unimportant, so far as blood transfusion is concerned, especially when one considers that there were but four deaths directly attributable to the transfusion in the 10,242 cases cited. This gives a death rate of 0.39 per thousand transfusions. I know of no other procedure in medicine or surgery in which the death rate is as low, and I believe it proves that our present procedure of choosing blood donors is the method of choice.

A METHOD FOR THE STUDY OF BONE MARROW CYTOLOGY. ABRAHAM S. GORDON (by invitation).

The purpose of this work was to study the elements of the bone marrow from a number of angles, such as the determination of the quantities of the different types of cells per unit volume of bone marrow, the relative proportions of the various types of elements to one another, and the character of the different types of cells in their various stages of differentiation, hoping possibly to follow these stages to their origin in the form of the primordial cell or cells.

In the quantitative estimation of the cellular content of the bone marrow, the principle used was the same as that for counting the cells in the circulation: an acetic acid solution for the nucleated elements, and a citrate solution for the red cells, as well as for all elements. The method may be termed "the dilution method." In all cases only rib marrow was used for the quantitative estimation. In most cases a 1:9 dilution of the marrow was used, which gave a suitable solution for counting and a convenient factor for calculation. Some cases required a modification of this proportion.

Special 3 by 3/8 inch (7.62 by 0.95 cm.) graduated tubes were used. One of these contained 0.9 cc. of the acetic acid solution, and another 0.9 cc. of the citrate solution. To each of these tubes 0.1 cc. of rib marrow was added, and the tubes were shaken for about fifteen minutes. The solutions were then drawn up into the proper blood-counting pipet to the 0.5 or 1 mark, as the case required, and the rest of the pipet filled with the appropriate solutions. The pipets were

again shaken for about ten minutes, and the counts made in the Neubauer hemocytometer. The calculations were made accordingly.

In all cases the total number of all cells and the total number of nucleated cells were counted separately from the different pipets in different counting chambers. Then the total number of red cells and the total number of nucleated cells were counted separately in the same chamber, and the two independent figures for the nucleated cells from the two different solutions were compared. In no case were the final figures recorded unless the separate figures corresponded, allowance having been made for the average technical error. All nucleated cells were counted in one group, comprising all myeloid cells, all nucleated red cells, including normoblasts, megaloblasts, and still earlier forms of the erythroid series, and all lymphoid cells, as well as endothelial cells and all forms of unclassified cells. In some cases, when indicated, the megakaryocytes were counted separately. The further subdivision of these cells becomes a problem for differential study, for attempts were not made to differentiate the various types of cells in the counting chamber.

In the differential study, blood serum was used for dilution. Autogenous serum, of course, would have been ideal, but as this was not always procurable, the blood group of the person was determined from the marrow, and the corresponding serum was used for dilution. The proportion of serum to marrow cannot be fixed for use in all cases as each marrow requires an amount commensurable with its own physical characteristics, and the proper quantity to be used must be judged from experience. Sometimes several mixtures must be made before a proportion is obtained that gives the proper smears. The Romanowsky dyes were used for staining. In some cases, such as myeloblastic leukemia, lymphatic leukemia, agranulocytic angina, aplastic anemia or any other form of severe anemia of unknown etiology, the results were counter-checked with the supravital stain and the oxydase stain, but these were not used for control in all cases.

DISCUSSION

MAX LEDERER: The method was developed originally from the way in which our routine bone marrow studies are made. The entire rib is removed and grasped between two pairs of strong forceps especially made for that purpose, and the contents are squeezed into Helley's fluid. It is surprising how much marrow can be obtained from a rib, except in elderly people in whom the ribs are fragile. However, if care is taken, the rib does not fracture. The marrow flows easily and can be sucked into a pipet. The idea occurred to Dr. Gordon of using isoserum for a person of the same blood group to which the patient belonged in making smears. At first he used a serum from groups A, B, AB and O respectively, but he learned later that serum from group AB could be used, since it contained no agglutinins. This serum can be kept in stock. The slide preparations show the detail of various cells to a fine degree. The method has not been presented for the purpose of pointing out diagnostic differentiations pathologically at this time, but rather to stimulate studies and collect information from which practical conclusions can be drawn. This is important in view of the fact that studies of bone marrow in the living subject are being adopted as a diagnostic procedure, and it is essential that concentration of the individual bone marrow cell be studied, by the method described or a similar one. Postmortem material lends itself to this work very well. Up to the present time, a series of 100 cases has been studied, but far more material must be collected before any definite conclusions can be arrived at. The two methods are presented for further clinical study. If they are of any benefit, well and good; if not, they will be discarded; they must stand or fall on their own merits.

LOUIS GROSS: I should like to ask Dr. Gordon whether he experienced any technical difficulty in sucking up bone marrow into a pipet, particularly fatty bone marrow. I should also like to know whether he made a series of counts on sections from different parts of the rib. I presume he did. If so, was any appreciable variation found in these counts?

ABRAHAM S. GORDON: Sometimes it takes hours of working with a specimen before a suspension is obtained that will give a uniform smear. Some marrows are easier to work with than others. Children's marrows are, as a rule, much easier than adults'. The principal thing is to mix the marrow with a definite amount of serum. The exact amount depends on the type of marrow. Some marrows have much fat in them. After thorough mixing, the fat will rise to the surface. This will answer Dr. Gross's question of the difficulty of sucking up the solution from fatty marrow. We have no difficulty there because the fat rises to the surface of the solution, so that it can be removed easily. The removal of the fat does not interfere with the counting process, nor with the final results, because we are starting with a definite volume, and the cellular content of the original volume is still present. We take the entire marrow, with the fat and blood.

As to counts from different parts of the rib, we have taken marrow from every part of the rib, from each end and from the center, and sometimes from different ribs of the same patient, and have found no appreciable difference in the results. When the marrow is squeezed out of the rib, a certain amount is allowed to run out; thus an average of the marrow in the rib is obtained. If any destruction is taking place, especially of the red cells, it cannot be helped, nor can it be avoided.

Interesting observations were made, and some of the results were uniform. If there is an acute infection before death, the marrow will present a definite picture. If there is no acute infection and the patient dies from some chronic disease or infection, the marrow will present another type of picture, and the cell content of the marrow will be almost constant. I do not know how constant it will be for different types of disease, age and sex. In the study that Lossen made of infants and children, there was also a great variation in the numbers, ranging from 200,000 or 300,000 to over a million. He was dealing with a more constant type of marrow, namely, acute infectious diseases in children, conditions in which the count should be higher and more uniform. Generally, we get a good idea of the bone marrow contents, both from the differential study and from the total number of cells.

MARKED DILATATION OF THE LEFT AURICLE OF THE HEART. EDWARD A. BURKHARDT, JR. (by invitation).

An Italian, aged 23, presented symptoms of acute cardiac decompensation. The patient was found in a stuporous, semimoribund state, with extreme dyspnea and cyanosis. Physical examination showed a margin of cardiac dulness extending 5.0, 5.0 and 8.5 cm. to the right of the midsternal line in the second, third and fourth intercostal spaces respectively. The apex beat was 132 and the radial pulse 112 per minute. Marked presystolic and systolic murmurs were present over the precordia. The patient died thirty-two hours after observation. Autopsy showed that the heart weighed 540 Gm. The left auricle was dilated to the right of the right auricle for a distance of 8.0 cm. to the right of the midclavicular line at the fourth rib. Dilatation to the left was limited by the arch of the aorta. The left auricle had a capacity of 593 cc. of fluid (after fixation). The auricle contained a thin mural thrombus and the mitral valve was stenosed to a slitlike opening, 2.2 cm. in length. Increased intra-auricular pressure through an incompetent mitral valve plus a damaged auricular myocardium probably account for the marked left auricular dilatation.

LYMPHOSARCOMA WITH INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM. CHARLES DAVISON and JOSEPH J. MICHAELS, Detroit (by invitation).

The brain and the spinal cord are rarely the seat of direct invasion by lymphosarcomatous masses. Occasionally the structures about the central nervous system, such as the bones of the skull or the vertebrae, may show the presence of lymphosarcomatous nodules. The scarcity of cases showing secondary involvement of

the nervous structure, especially the report of only one case in the literature in which the spinal cord was compressed, is the reason for this presentation.

Since 1922, twenty-six patients with lymphosarcoma were admitted to the Montefiore Hospital. Of these, seven cases presented neurologic signs, four of

Cases of Lymphosarcoma with Involvement of the Nervous System

No.	Sex* and Age	Duration of Illness	Onset: General Symptoms	Onset: Neurologic Signs	Clinical Diagnosis	Neurologic Diagnosis	Response to Deep Roentgen or Radium Treatment	Results of Autopsy or Biopsy
1	♀ 61	1 year, 9 months	Gradual	Gradual	Lymphosarcoma	Extramedullary neoplasm	Improvement early without any response later (deep roentgen ray only)	Generalized lymphosarcomatosis, with metastasis to dura
2	♂ 40	1½ years	Sudden	Sudden	Lymphosarcoma; hydrothorax	Herpes zoster	Relief early; no response later (deep roentgen ray only)	Generalized lymphosarcoma; pleural effusion; extramedullary neoplasm
3	♂ 32	9 months	Sudden	Sudden	Neoplasm of the right lung	Metastasis to cord; possibility of subacute combined degeneration	Early improvement; no response later	Lymphosarcoma of right lung; empyema; extramedullary deposits
4	♂ 45	1 year, 11 months	Sudden	Sudden	Generalized lymphosarcoma	Generalized lymphosarcoma with involvement of the meninges at the base of the skull	Temporary remission of glandular enlargement early; pain was not relieved	Generalized lymphosarcomatosis, with invasion of the middle and posterior fossae
5	♂ 64	Discharged in 1922 and not heard from since	Sudden	Sudden	Lymphosarcoma	Lymphosarcoma with invasion of the posterior cranial fossa	Early improvement, with recession of enlargements and symptoms	Biopsy: lymphosarcoma
6	♂ 37	7 months	Sudden	Gradual	Lymphosarcoma of the left lung with metastasis	Lymphosarcoma with metastasis to the vertebral column	Improvement early, with no response later (roentgen ray and radium)	Pleural exudate containing tumor cells
7	♀ 38	8 months	Sudden	Sudden	Lymphosarcoma of the neck	Left peripheral facial palsy	No benefit from either roentgen ray or radium	Biopsy: lymphosarcoma

* In this column, ♂ indicates male; ♀, female.

which were verified postmortem. Three of the cases presented signs of compression of the spinal cord, the remaining one showing involvement of the brain.

Of the seven cases showing neurologic signs, two showed invasion (cases 4 and 5) of the cranial cavity localized chiefly in the middle and posterior fossae; four showed involvement of the vertebral column or the spinal meninges causing compression of the spinal cord or on the posterior roots resulting in herpes zoster (as in case 2), and one case involved the facial nerve peripherally (case 7).

Cases 4, 5 and 7 showed early involvement of the cervical lymph nodes; in two instances (cases 4 and 5) there was invasion of the cranial cavity. In the other cases the invasion of the glands of the neck did not occur until late in the disease.

In case 4, in which the cranial cavity was invaded, the brain tissue itself did not show any evidences of invasion by the lymphosarcoma, as usually seen in metastasis from other tumors, especially metastatic carcinomas. The invasion in this case took place by way of the lymphatics. As the brain proper is not supplied by lymphatics this readily explains the absence of invasion of the brain tissue by lymphosarcomas. The cases showing involvement of the spinal cord in the form of compression did not show enlarged cervical lymph glands until late in the disease. In none of these cases was the spinal cord directly involved.

Except for case 7, all of the seven cases in which deep roentgen and radium treatment was given showed a recession of the lymphosarcomatous masses, with improvement in the symptoms only early in the treatment. After a few treatments the enlargements and symptoms recurred and finally failed to respond. This is characteristic of all the lymphosarcomas.

The following conclusions were given: Twenty-six cases of lymphosarcomas observed in the Montefiore Hospital since 1922 were investigated, seven of which presented neurologic signs and symptoms.

2. In none of the cases was there a direct invasion of the brain or the spinal cord. The symptoms were due chiefly to compression from invasion of the skull, vertebrae or meninges.

3. Invasion of the cranial cavity took place only when the cervical lymph nodes were involved, and as observed in our series, when they were involved early.

4. Deep roentgen and radium treatment, while not a cure for the disease, gives some relief from the symptoms during the first few applications. The relief is chiefly due to the recession of the tumor which causes compression on the respective organs. When these enlargements fail to respond to treatment, improvement in the symptoms may not be expected. These cases, however, for a period of time are benefited a great deal by deep roentgen rays or radium. At present these are the best forms of palliative treatment.

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 9, 1929

HENRY C. SWEANY, *President, in the Chair*

EXPERIMENTAL FAT NECROSIS AND ISOLATION OF A CAUSATIVE FACTOR.

M. PINSON NEAL and MAX M. ELLIS.

A lipase fraction has been isolated from fresh hog's pancreas, dried pancreatin (Armour's lot no. 205257) and the dried seeds of *Arachis*, the peanut, and *Helianthus*, the common sunflower. The lipase fractions from each of these sources when injected intraperitoneally into white rats produced definite fat necrosis.

These lipase fractions were not thermostabile, and were rendered inactive, so far as the production of fat necrosis was concerned, by treatment with ethyl alcohol in strengths above 50 per cent; they were water-soluble and were not injured by the presence of ether, toluene or xylene; they were not adsorbed by blood or animal charcoal, from either acid or alkaline solutions; they were extracted from both acid and alkaline material, and they did not digest fibrin, but were active in the splitting of ethyl butyrate.

The results obtained by injections of these extracts which had no effect on fibrin permit the conclusion that trypsin is not required in the production of experimental fat necrosis.

Histologic lesions of fat necrosis found six hours following injections of the lipase fraction derived from *Arachis,* in morphology and in staining reaction, showed damages to cell walls, cytoplasm, nuclei and cell fat content. Loss of nuclear material within six hours after injections showed, so far as the cell was concerned, the critical character of the process. The loss of nuclear material appears to be entirely by lysis. The earliest anatomic lesions were found sixteen and one-half hours after injections of the lipase fraction from hog's pancreas. Gross and microscopic lesions eight days after injections of *Arachis* material showed definite reparative reactions. The local limitation of the lesions of fat necrosis can be partially accounted for by the cellular wall, or zone of demarcation.

This experimental fat necrosis produced no definite clinical manifestations in the animals into which injections were made.

The assumption of Langerhans that lipase is an etiologic factor of fat necrosis has been proved experimentally by the use of lipase fractions derived from animal and vegetable materials.

DISCUSSION

H. G. WELLS: I wish to congratulate the authors on the splendid piece of work they have presented. I am, of course, particularly interested because for several years more than a quarter of a century ago I tried to find out what it was that caused typical fat necrosis, and, with the means at that time available, I was unable to separate a lipase from trypsin and still produce fat necrosis with a lipase. Blood and extracts from liver which are actively lipolytic would not produce fat necrosis. I thought that this might depend on the fact that there are several sorts of lipases, some of which hydrolyze one sort of ester and not another. I noted that Dr. Ellis spoke only of testing his lipases with ethyl butyrate. Did he determine whether they would hydrolyze triglycerides? Of course, in order to produce fat necrosis the lipase would have to hydrolyze triolein and tripalmitin. In the experiment in which the lipase was inactivated by alcohol, was there found to be close parallelism between the loss of ability to produce fat necrosis and the loss of fat-splitting activity? Of course, the crucial experiment here was the production of fat necrosis with artificial lipases prepared by Falk's method. Here certainly the presence of trypsin, either active or inhibited, can be excluded. In Dr. Neal's presentation no mention was made of the lesions produced by these artificial lipases, and I should like to know more about the effects they produced. Were areas of fat necrosis found in the thoracic cavity in these experiments? I have often seen them in fat necrosis produced by intraperitoneal injection of large doses of active pancreatic extracts.

M. M. ELLIS: The lipase fractions did hydrolyze triglycerides. In the alcohol treated extractives there was a parallelism between the loss of the fat-splitting ability and the property to produce fat necrosis; as the fat-splitting activity declined, so did the fat necrosis producing property. Experiments using the artificially prepared lipase fraction (following Falk's method) are in progress, and while the observations are suggestive, we are not prepared to give a final statement. Regions of fat necrosis were not found in the thoracic cavity of any of our 300 animals into which intraperitoneal injections were made.

M. P. NEAL: In the presentation of the pathologic phase of this work mention of the lesions produced by the artificial lipases was intentionally avoided because our observations to date are not considered conclusive.

SQUAMOUS CELL CARCINOMA OF THE TRACHEA. PAUL J. BRESLICH.

A white man, aged 60, complained of severe dyspnea of two days' duration. For six months he had had paroxysmal attacks of dyspnea occurring with increased frequency usually at night. There was also a persistent productive cough with hoarseness. There were no significant observations in the physical and roentgen examinations of the chest. Treatment failed to relieve the dyspnea and the patient lost strength rapidly. The postmortem examination disclosed a tumor in the

posterior wall of the trachea just above the bifurcation which narrowed the lumen to a slit a few millimeters wide. The tumor extended backward to the prevertebral fascia displacing the esophagus to the left. The surface of the tumor in the trachea was nodular and ulcerated, while the esophageal mucosa over the bulging mass was smooth and unchanged. Except for a small nodule in the lining of the esophagus just below the tumor and covered with smooth mucosa there were no metastases to other tissues. There was no evidence of an esophageal diverticulum or tracheo-esophageal fistula from which the tumor might have originated. The new growth seemed therefore to be primary in the lining of the trachea. The cells of the tumor were squamous epithelium, and in the literature are reported seven similar growths of the trachea.

(The complete report will be published in the *Journal of Cancer Research.*)

DISCUSSION

H. G. WELLS: In a case of carcinoma of the trachea with squamous cell structure, the exclusion of a primary carcinoma of the esophagus invading the trachea is difficult. I noticed that in the specimen passed around the esophagus is involved. I take it that the conclusion that this carcinoma arose in the trachea rather than in the esophagus rests on the lack of ulceration in the surface of the esophageal growth. Were there malignant changes in the deeper portions of the esophagus lining?

E. R. LECOUNT: Growths arising from esophageal diverticula need consideration.

E. F. HIRSCH: The conclusion that this tumor probably arose in the trachea or possibly contiguous tissues but not of the lining of the esophagus was reached because a bulky ulcerated tumor was found occluding the lumen of the trachea; because the two submucous nodules of the esophagus were much smaller, were covered by a smooth mucosa and had the appearance of small metastatic nodules, and because the stratified squamous epithelium of the esophagus covering the nodules examined in a number of places was regular and the deeper portions nowhere invaded the submucosa.

POLYPOID PERICARDITIS. MILTON G. BOHROD.

A white man, aged 27, died of cardiac decompensation following an old, partly calcified mitral and aortic endocarditis. Hanging into the pericardial sac from the point of reflection of the parietal pericardium from the right auricle posteriorly, there was a mass consisting of several dozen polyps, some of them solid, most of them filled with blood in various stages of inspissation and with various degrees of organization. The blood spaces were lined by a single layer of endothelium. The walls of the cysts contained macrophages filled with blood pigment.

The tissue between the polyps was loose and fibrillar, with many capillaries, and with many large pale cells resembling macrophages. The latter were often grouped into nodules about a blood vessel, thereby resembling Aschoff nodules. On the surface epicardium and on many of the polypi there were accumulations of fibrin and red blood cells.

This case seems to illustrate a peculiar mode of healing in a rheumatic pericarditis. No such polypoid mass has ever before been reported. The polypi are probably formed by the fusion of partly organized fibrin masses, the gaps between them having previously become lined by endothelium. Small endothelial lined spaces are common in a healing pericarditis, and occasionally small cysts are seen. Lanche has reported the presence of a few cysts the size of a pea in one case. The blood in the polyps seems to have come from a previous hemopericardium.

DISCUSSION

E. R. LECOUNT: The title is rather unfortunate in suggesting another variety of inflammation. Organizing pericarditis with multiple polypi might be better.

Book Reviews

DIE FRAGE NACH DEM URSPRUNG DER ENDOMETRIOIDEN HETEROTOPIEN BEIM GESCHLECTSREIFEN WEIBE. By KONRAD HEIM, Privatdozent für Geburtshilfe und Gynäkologie, Oberarzt an der Klinik. Aus der Universitäts-Frauenklinik Leipzig. Berlin: S. Karger, 1929.

In this monograph Heim, of Leipzig, undertakes an analysis of all types of endometrial heterotopy in the sexually mature woman, using the term heterotopy in the broadest sense so as to include adenomyosis uteri externa as well as intrauterina and differentiating sharply between blastomatoid adenomyoma and adenomyosis. He reviews the various theories of origin of these growths, including the mesonephros hypothesis and the fetal derivation, with a detailed description of the embryologic development of this area.

The postfetal theories are discussed at much length: the direct origin of adenomyosis uteri interna from endometrium (Cullen), the serosal epithelial theory of Iwanoff, Meyer, Lauche, and Fischel, the transplantation theory of Sampson and the Halbanian theory of metastatic hystero-adenosis.

The author's own material consists of eighteen cases in women between the ages of 25 and 50, of adenomyosis rectovaginalis, adenomyosis uteri externa, adenomyosis externa des ligamentum rotundum, tubal adenomyosis and adenomyosis interna. Chocolate cysts of the ovaries were not always found. The main purpose of the monograph is obviously an attack on Sampson's implantation theory, and since Germany is the stronghold of its antagonists, all the Teutonic artillery is arrayed against it. Heim considers each of the arguments given by Sampson in support of the latter's explanation of many ectopic endometrioses. Sampson found the condition in about 20 per cent of all his gynecologic patients. Heim finds no parallel for this figure in German surgical statistics. In two large institutions in which he had personal opportunity to look over the records and in which from time to time a special outlook for these conditions was kept he was able to encounter only a modest amount of material as compared with what he calls the fanciful, imaginary American numbers (den phantostisch anmutenden Amerikanischen Zahlen)? The fact that endometrial heterotopy is encountered only during menstrual life he thinks can be utilized just as easily to support a serosal epithelial metaplasia by accepting special hormonal changes. "Uterine mucosa-like is by no means uterine mucosa. . . . Robert Meyer's antipathy to expressions such as endometriosis, endometrioma, etc. is based upon such reserved judgment."

The author sees little support for the implantation hypothesis in the location of many growths about the tubal funnel. Also the idea that normal body cells can be pulled from their foundations simply by a needle prick or suture and be able to grow in a strange and new environment he regards as purely speculative. He admits, however, that most of the mechanical prerequisites for the implantation theory are adequately fulfilled.

The biologic suppositions involved in the acceptance of the viability and transplantability of menstrual desquamate are considered the crux of the Sampsonian idea. The investigations of Sekiba of Aschoff's institute and of Bohnen of Schroeder's clinic are reviewed and the author's own work on the strata of the desquamation is presented. Heim admits great variation between persons and also in the same person. In all the large tissue fragments studied as early as they loosened themselves (sic) he found histologic signs of necrobiosis. The shedding appeared to continue down to the basalis, which showed no changes. The lack of vitality of menstrual desquamate he believes proved beyond all doubt.

The experimental transplantation of endometrial tissue by Jacobsen, Albrecht, Katz and Szenes, Michon and others carries little weight with the author since the endometrial fragments used were not from menstrual desquamate. Heim attempted

in vitro culture of human uterine mucosa from menstrual and intermenstrual periods and obtained a lively growth of cells which apparently he was not able satisfactorily to classify. Cron and Gey are criticized as being too easily convinced of the epithelial nature of cells growing in their menstrual cultures.

The monkey, naturally, is regarded as the best of the lower animals for the experimental study of endometrial heterotopy. Heim used five monkeys, two of which died, leaving one mangabe and two rhesus for study. He (1) sowed the superficial layers of their decidua menstrualis in the peritoneal cavity, (2) established a fistula between the uterus and pelvic cavity during menstruation and (3) planted fresh human menstrual sequestrums on the peritoneum or on the ovarian serosa of the sexually mature female monkey and at the same time injected ovarian hormone. After forty-one, forty-eight and sixty-two days no endometrioidal growth was obtained in any of the three animals. It might be added in parenthesis that recently Fraser (*J. Obst. & Gynaec. Brit. Emp.* **36**:590, 1929) reported the first case of spontaneous endometriosis in a monkey, *Macacus rhesus*. Hence after considering his anatomic studies and transplantation attempts Heim concludes that fragmented menstrual tissue has no growing power and that Sampson's theory while theoretically admissable is of doubtful validity. He quotes Robert Meyer as stating with sorrow that Sampson should be so assuming in the choice of his proofs, referring specifically to the latter's well illustrated article on embolic endometriosis which contained many unretouched photomicrographs of endometrial fragments in uterine venous sinuses (*Am. J. Path.* **3**:93, 1927). Identical preparations were sent to Dr. Meyer who considered the evidence as nothing more than contamination or dirt.

The photomicrographs in Heim's monograph are poor, being almost uniformly out of focus and thus do not add much strength to his argument. The article is otherwise a well presented statement of the views of the protagonists of the Robert Meyer theory of serosal metaplasia.

HOOKWORM DISEASE, ITS DISTRIBUTION, BIOLOGY, EPIDEMIOLOGY, PATHOLOGY, DIAGNOSIS, TREATMENT AND CONTROL. By ASA C. CHANDLER, PH.D., Professor of Biology, Rice Institute, Houston, Texas. Price, $5.00. Pp. 494, with 33 illustrations. New York: The Macmillan Company, 1929.

"There is probably no important and widespread human disease in which so many important and diversified contributions to knowledge have been made within a decade as has been the case with hookworm disease." To this introductory sentence of the author's preface might well have been added the statement, that among the most important of these contributions stands the long series of articles on almost every phase of the hookworm problem published by Dr. Chandler from 1924 to 1929. These researches admirably prepared him for the task of bringing together the recent advances in the knowledge of hookworm disease, which are embodied in a widely scattered, complex and voluminous literature. The work of gathering together and digesting the information from this recent literature has been thoroughly done, apparently nothing of any importance having been missed. The extent of this task is shown by the fact that the author makes direct reference in the text to more than 300 papers published in the last ten years.

In considering these recent researches, Dr. Chandler does not hesitate to stress definitely his own opinion on matters of controversy. This does not seem in the least objectionable to the reviewer perhaps because he finds himself in substantial agreement with practically all of the views expressed. In every case, at any rate, the impression is gained that the other side of such controverted questions is given a fair hearing.

The keynote of the whole book is the quantitative consideration of hookworm infestation. This involves emphasis on the worm burden of the population group as measured by some egg-counting method. Much, therefore, is made of the significance of carriers and subclinical infestation and the inadequacy of incidence statistics used alone. While the few who still react against this point of view

will find much to argue against in almost every chapter, the author is correct in saying that he expresses the attitude of most of the recent investigators in this field.

The book surveys in detail every phase of the hookworm problem, giving on the whole an adequate conception of the present status of knowledge. While it would take too long to comment on every chapter, there are certain parts of the book that should be given special mention. The chapter on geographical distribution goes far beyond anything now available in the literature on the relative importance of hookworm disease in different parts of the world. In making his distribution maps, the author has used the knowledge of the factors limiting hookworm dissemination to supplement present knowledge. While, as the author himself states, these maps will undoubtedly have to be modified in detail as new information becomes available, they give by far the best picture at present of hookworm disease as a world problem.

The two chapters on epidemiology give a worldwide view of the relative importance of the influence of climate, soil, race, occupation and human habit on the dissemination of hookworms. While no two workers will agree on every detail of interpretation, this account gives a good idea of present knowledge and should stimulate workers the world over to publish new observations. The detailed account in the appendix of the various methods that have been used in studying the hookworm problem is one of the most valuable parts of the book.

The full bibliography of recent researches for the first time brings together in one place a list of the important contributions to this subject of the last ten years. In citation of references in the text, the book is handled as a monograph rather than a textbook which adds much to its value, especially to the research worker.

Although perhaps the text could have been somewhat condensed in places, the book as a whole is written in a clear and interesting style and is unusually free from typographic errors. It ought to go far in giving medical men and parasitologists a better idea of the present status of knowledge on this important disease.

THE IMMUNOLOGY OF PARASITIC INFECTIONS. By WILLIAM H. TALIAFERRO, PH.D., Professor of Parasitology, the University of Chicago. Price, $6. Pp. 414. New York: The Century Company, 1929.

As stated in the preface, this book is a compilation and evaluation of the results of the immunologic work on animal parasites and diseases caused by them. It is the first book of its kind. Chapter 1 reviews the concepts of parasitism, infection and immunity. Chapter 2 is devoted to a discussion of the serologic reactions used in diagnosis in diseases caused by animal parasites: amebiasis, leishmaniosis, trypanosomiasis, etc. In hydatid disease of man and trypansomiasis of horses complement fixation has reached a high degree of usefulness and promises to become of value also in the human schistosome invasions. In kala-azar, the visceral form of human leishmaniosis, specific serologic tests do not appear to be of diagnostic value, but certain nonspecific tests based on the increase of euglobulin in this disease are giving consistent results. Chapter 3 deals with the lysins and the antibodies that inhibit reproduction of the parasites in trypanosomiasis and bird malaria. Chapter 4 discusses the protective and curative actions of immune serums in certain protozoon infections and trichinosis, and chapter 5 takes up hypersensitiveness and the cutaneous tests for detecting parasitic invasions, more particularly in hydatid disease and ascariasis. In chapter 6 the production of symptoms by animal parasites is considered. The single undoubted toxin produced by animal parasites is the sarcocystin of *Sarcosporidia*. Allergy may play a rôle in parasitic symptomatology; *Ascaris* pneumonia, for instance, appears to be an allergic reaction. In chapter 7, the cellular basis of immunity in parasitic diseases is reviewed, and chapters 8 and 9 deal with the nature and production of immunity in parasitic diseases and with the immunologic reactions for classifying animal parasites. In the appendix is a helpful list of the presumably valid names, com-

mon synonyms and common hosts of the parasites considered in the text. The bibliography "has been made as complete as possible," and there is an index of authors as well as of subjects.

Taliaferro's book is well written. The presentation is clear, reliable and scholarly. There are remarkably few errors. It reflects credit to the American school of parasitology. The scope and nature of its contents have been set forth in some detail to show its significance to the parasitologist as well as to the immunologist. And the pathologist in the narrower sense can be aided by it in many practical and other ways. It is an important contribution to parasitology and to immunology and will be a stimulus and guide to workers in both sciences.

EPIDEMIC ENCEPHALITIS: ETIOLOGY, EPIDEMIOLOGY, TREATMENT. Report of a Survey by the Matheson Commission: William Darrach, Chairman; Haven Emerson, Frederick P. Gay, William H. Park, Charles R. Stockard, Frederick Tilney, Willis D. Wood, Hubert S. Howe, Secretary. Josephine B. Neal, Director of Survey, Helen Harrington, Epidemiologist. Price, $3. Pp. 849, including bibliography and author and subject indexes. New York: Columbia University Press, 1929.

In this book are recorded the results of a survey of the work on the etiology, treatment and epidemiology of epidemic encephalitis. Closely allied subjects—postvaccinal encephalitis, herpes, encephalitis in rabbits—are considered also. Chapter 1 gives a summary of the investigations into the etiology of encephalitis. The chapter concludes as follows: "In spite of the vast amount of experimental work that has been done, there are still widely varying opinions in regard to the etiology of epidemic encephalitis. A comparatively small group believe that it is a toxic disturbance of the central nervous system. Another rather small group considers that a pleomorphic streptococcus is the cause. A somewhat larger number of investigators are convinced that a filtrable virus, identical with or closely allied to the herpes virus, is the specific agent. In view of these conflicting opinions, many are forced to the conclusion that the etiologic agent of epidemic encephalitis has not yet been definitely demonstrated." Chapter 2 deals with other types of encephalitis, including the postvaccinal. Chapter 3 reviews the treatment, and chapter 4, the longest of all, brings together the epidemiologic data of more than 9,000 cases. The strictly clinical aspects and the anatomic changes of the disease are not considered in detail. The bibliography, which is arranged conveniently, takes about half of the book. There is here a highly useful survey which we owe to the generosity of Mr. William J. Matheson, at whose instigation further studies have been started, the results of which will be published from time to time. The reviewer has heard the wish expressed by physicians that competent, minute surveys might be made of the occurrence of epidemic encephalitis during a certain time within definite and suitable localities, the idea being that some light might be thrown on the modes of spread and perhaps other aspects of the disease.

MEDICAL LEADERS FROM HIPPOCRATES TO OSLER. By SAMUEL W. LAMBERT, M.D., and GEORGE M. GOODWIN, M.C. Price, $5. Pp. 331, with 32 figures. Indianapolis: The Bobbs-Merrill Company, 1929.

This is a short résumé of the history of medicine in sixteen chapters, the central figures of which are outstanding leaders. Chapter 10, however, on quacks is an exception to this statement. The emphasis placed on the influence of the leaders whose work is discussed seems fair and adequate, but probably the significance of Claude Bernard as exponent of the experimental method in medicine is not emphasized sufficiently. The warning on page 267, not to call dead bacteria used to prevent typhoid fever a vaccine, is, of course, a slip, as is also the designation of a certain serum against pneumonia as "truly antitoxic." The illustrations reproduce mostly more or less classic engravings and photographs of great medical men. The style is clear, the presentation leans to the semipopular without being

too sketchy and the atmosphere throughout the book reflects the best medical ideals. The authors succeed well in tracing the significant steps in the progressive growth of medical knowledge and its practical application.

PRINCIPLES AND PRACTICE OF ELECTROCARDIOGRAPHY. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Price, $7.00. Pp. 220, with 61 illustrations. St. Louis: C. V. Mosby Company, 1929.

As one would anticipate, electrocardiography is presented more from the physiologic point of view. Medical students and others desiring an initial acquaintance with electrocardiography may receive adequate instructions in theory and practice from this volume. The clinical features are not neglected. The reviewer is a little disappointed in the fact that although a description of different types of electrocardiographic equipment was included, only indirectly is there any "critique of apparatus" which makes the volume by the same author on the "Circulation of Health and Disease" so valuable to experimenters in this field. Any investigator who is at all interested in experimental pathology of the cardiovascular system and who is not already familiar with recent developments in electrocardiography can readily obtain a background from this volume.